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CLINICAL
ENDOCRINOLOGY

VOLUME TWO

CLINICAL ENDOCRINOLOGY

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TWO VOLUMES

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CHAPTER 6

Testes

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SECTION 45

PRELIMINARY

I HISTORY

Before the Christian Era

About 1400 B C ^m

384 322 B C Aristotleⁿ

777 837 Mesue the Elder⁴¹
1664 Willis ^o

1667 Hamen and van
Leeuwenhoek ^o

1668 De Graaf¹⁵
Spallanzani⁶

1762 John Hunter³¹

1762 Pott⁵³
1786 John Hunter³⁰

1799(?) John Hunter³
1830 Cooper¹³

1841 von Kolliker⁶⁷
1849 Berthold³

1850 Leydig³⁷
1865 Schweigger Seidel⁶⁰
1865 Sertoli⁵

1877 Malassez, ⁴⁰ Monod and
Arthaud⁴⁴

— 1889 Brown Séquard⁷ ⁸

1891 Poehl ²
1893 Groffith⁻⁵

1894 Ramm³⁴

1895 Florence¹⁹
1896 Reinke⁵⁸

1899 Bevan⁴
1899 Sellheim⁸¹
1903 Albers Schonberg¹

1903 Bounin and Ancel³

Castration was practiced for many centuries and re-
sults were recognized

Testicular tissue was recommended for impotence⁹⁹
Castration effects in birds, beast and man were
described

Testicular extract prescribed as aphrodisiac
Blood receives a special ferment from the spermatic
veins

Sperm cells seen for first time
Lobular architecture of the testicle was demonstrated
Fertilization occurred by direct contact of sperma-
tozoa and ova

First experiments on transplantation of testes in the
fowl were performed

Recognition of hydrocele
Secondary sexual characteristics in birds and descent
of testes in humans were described

Successful artificial insemination of a woman
Epididymis of a dog contained active sperm 6 years
after ligation of vas

Sperm declared to be of cellular origin
First to prove internal secretion of testes normal
cock instincts were produced in capons by testicular
grafts

Interstitial cells were described
Spermatozoon possesses nucleus and cytoplasm
Spermatids attach to special supporting cells during
their development

Choriocarcinoma discovered
Effects produced by self administered testicular ex-
tracts (from dogs and guinea pigs) were reported

A substance, spermin isolated from testes
Degeneration of testicle by replacement within ab-
dominal cavity (dogs)

Castration used as a therapeutic measure for treat-
ment of prostatic hypertrophy

Test for detection of spermatic fluid
Crystalloids of interstitial cells found

Operation for undescended testicles first performed
Delay in union of epiphyses noted in capons

Certain amount of x ray or radium exposure over
testes caused sterility

Removal of one testis from a rabbit produced hyper-
trophy of the interstitial cells in the remaining one,
suggesting hormonal secretion

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INTRODUCTION

Skin manifestations of a disease of another organ or an organ system may be *specific* or *nonspecific*

Specific dermatomes contain the same pathological elements which cause or characterize the lesions of the disease in another part of the body system. Skin metastases of a malignant tumor of the stomach repeat the adenomatous structure of the primary growth. Leukemic infiltrations of the skin consist of the typical leukocytes of the leukemia and hematogenous tuberculosis of the skin is still as much tuberculosis as it was in the tubercular focus from which it descended.

Much more frequently the dermatomes are *nonspecific*. Neither anatomy nor course seem to repeat the primary disease. The pruritus in Hodgkin's disease, sweating in tuberculosis or in arsenic poisoning are such nonspecific manifestations. They are cutaneous responses to pathologic stimuli and since the means of expression which the skin possesses are limited, heterogeneous causes may produce identical skin symptoms. Pruritus, perspiration, erythema, pigmentation, hypertrichosis, allergic inflammation, keratosis are some words from the language in which the skin answers if it is provoked. It follows that a conclusion as to the underlying condition from a nonspecific symptom like pruritus alone is not possible. In other words the nonspecific dermatomes are *not diagnostic*; they are merely *suggestive* of a diagnosis. They have to be weighed together with other manifestations to make a diagnosis possible. Naturally this limits the practical value of the knowledge of the cutaneous symptoms of internal disorders. However, the same is true of the symptomatology of all other fields. A diagnosis is usually not based on one specific symptom but rather on a characteristic pattern formed by a *variety* of nonspecific manifestations.

Another fact increases the difficulty. Hardly one dermatome is an *invariable* companion of an internal disorder. The melanosis in Addison's disease is missing in a considerable percentage of the cases. Pruritus commonly encountered in Hodgkin's disease, diabetes, gout, arsenic poisoning may be absent. Even the rash in measles or chicken pox may not appear. Jaundice in obstruction of the common duct seems to be one of the few inevitable dermatomes.

Before entering the discussion of the skin manifestations of internal disorders the reader might well ask which *criteria* permit the assumption of such a relationship.

There is no doubt about the relation of the specific dermatomes to the internal companions to which they are *subordinated* as in the case in focal infection or *coordinated* as in syphilis. For the investigation of the status of the nonspecific dermatomes the statistic method is the most important one. If pruritus is associated with diabetes in a larger percentage than with a normal control

group we are justified in calling pruritus a dermatome of diabetes. This apparently simple method naturally has all the fallacies connected with statistics. The number of cases must be sufficiently large. The character of the material must be considered. For example in the case of diabetic pruritus it is important whether the patients are hospitalized or ambulatory, controlled or uncontrolled diabetics, wealthy or poor. The control group must be large and its character should correspond to the probed group of diabetics in age, sex, racial and social make up, etc. It is of greatest importance whether observations have been gathered from records which had been written by another physician or whether they have been collected by the author himself with the purpose of his investigation in mind. Generations of interns may not have paid much attention or at least may not have entered a note on the presence or absence of pruritus or epidermophytosis in the diabetic patients. Then a man becomes interested in the question and he starts to ask patients and to make notes. This may cause the apparent incidence to soar.

If rare dermatoses occur in association with relatively rare internal diseases the relationship can be accepted if a few cases only have become known. Examples are the few instances of dermatitis herpetiformis after total parathyroidectomy or cutis verticis gyrata in acromegaly or acanthosis nigricans in visceral carcinoma.

Other criteria of a relationship between a dermatosis and an internal disorder are disappearance of the former following successful treatment of the latter as it occurs in some cases of hypertrichosis of ovarian origin. The close parallelism between the ups and downs of the disease and the skin changes is sometimes a good evidence of a relationship. This can be observed in the dermatoses of the legs which sometimes accompany periods of circulatory decompensation.

Skin Manifestations of Internal Disorders

CHAPTER I

THE DERMADROMES OF SYSTEMIC INFECTIONS

Hematogenous or Metastatic Infections * Microbids (Bloch¹⁷)

The ectogenous infections of the skin for example impetigo erysipelas and the superficial mycoses do not belong to the subject of this book. If however the micro organisms travel with the blood stream from an infectious focus in the system to the skin and cause there corresponding manifestations of the infection the resulting dermatosis is a dermatome of the systemic infection and requires discussion.

When as far back as 1915 J. Jadassohn*¹⁸ gave this definition of hematogenous skin infection he wisely chose the word corresponding. He was aware of the fact that the hematogenous infections are not identical with the primary lesion. They differ more or less although a relationship can usually be found. The various hematogenous infectious lesions the microbids (Bruno Bloch) or the bids for short have been shown to have a number of common features. The study of the experimental hematogenous infection of the guinea pig with fungi proved particularly instructive for the understanding of the pathogenesis of the microbids in general.

Experimental Hematogenous Fungus Infection—Saevs¹⁹ in J. Jadassohn's clinic in Berne Switzerland was the first to show that a single intracardial injection of an emulsion of spores of *Achorion quinckeum* and *Trichophyton gypsum* can produce in the guinea pig several crops of fungi containing clinically typical skin lesions. These mycotic lesions healed spontaneously after about three weeks. The hematogenous skin infections differed little from primary skin infections. The animals developed a generalized specific skin allergy toward fungi just as they did after ectogenous infection. The hematogenously produced lesions appeared to have a certain predilection for shaved or traumatized²⁰ sites.

The hematogenous infection of the skin have been studied intensively by Joseph Jadassohn and Bruno Bloch and their pupils.

¹ Bloch B. Les microbides cutanés. Arch. f. Dermat.-syphill. Hôp. St. Louis 4: 157-193, 1913.

² Saevs J. Experimentell Beiträge zur Dermatomykose. Arch. f. Dermat. u. Syph. 121: 161-191, 1915.

³ Kogoj F. Lokalisationsbestimmung hämatogener Infektionen. Arch. f. Dermat. u. Syph. 130: 333-355, 1916.

M Sulzberger²⁰ then in Bloch's clinic could show that no actual mycotic granuloma of internal organs could be produced by intracardial injection of *Achorion quinckeum* in spite of the presence of fungi in the spleen and in other organs. The histologic examination of hematogenous skin lesions demonstrated that the fungi could be found mainly in the stratum corneum and in the hairs not in living tissues²¹ leaving no doubt about the *elective localization* or *dermatotropism* of certain microbes.

Foci—The foci from which the microbes may enter the blood can be found in many organs. Streptococci and staphylococci are known to occur in dental granulomas in abscessed teeth and in many other organs. The lungs and the mediastinal lymph nodes may be the foci for the hematogenous spread of tuberculosis. The skin itself may be the site of primary foci which are able to emit fungi, tubercle bacilli and other microbes into the system. Trauma, inflammation with hyperemia and suppuration (kerion), fever and intercurrent infections like colds or influenza are likely to have an influence on the mobilization of microbes from a primary focus. X-ray treatment of a primary trichophytic lesion and injection of trichophytin are named among the factors which have been seen to provoke trichophytids.²² The traumatization of gonorrheic infiltrates or tuberculous tissues may cause a crop of hematogenous skin infections. All infectious processes which lead to erosion of blood vessels and lymphatics may lead to metastatic infection. Jadassohn² stresses the importance of all influences which weaken the systemic resistance. The possibility of a release of bacteria from a silent focus into the blood stream apparently without any of the known causes must be considered.

The presence of microbes in the blood in cases of microbids has been demonstrated for fungi by M. Jessner²³ and others⁴ and for tubercle bacilli by Kren and Löwenstein²⁴ Konrad²⁵ and others. Many similar findings especially of pyogenic bacteria are known.

Metastatic Sites—The experimental fungus infection shows that the microbes do not stay and develop wherever they are deposited by the blood stream. The fungi prefer the keratinized tissue, other microbes favor other sites. Tuberculids are seen most often on the extremities especially the legs probably due to the tendency to stasis in the extremities. Some epidermophytids have a special tendency to form eczematoid epidermophytids in the palm. Traumatized or inflamed areas attract fungi, spirochetes, pyogenic bacteria or

²⁰Sulzberger M. Pathogenesis of Trichophytids. The Spontaneous Passage of Formed Elements from the Primary Lesion into the Circulating Blood. Arch Dermat & Syph 88: 891-901 1928.

²¹Bloch B. Allgemeines und experimentelle Biologie der Dermatomykosen. Handb d H u Gk 11: 300-377 1925.

²²Jadassohn J. Importance of Immune Biologic Processes in Morphology of Skin Lesions. Arch Dermat & Syph 21: 35, 1930.

²³Jessner M. Trichophytid. Zbl 11: 449 1924.

²⁴Bloch B. Die Trichophytide. Handb d H u Gk 11: 564 1925.

²⁵Kren O and Löwenstein E. Die Bedeutung der Bakteriämie bei den verschiedenen Formen der Hauttuberkulose und bei Lupus erythematosus. Arch f Dermat u Syph 166: 375-389 1932.

²⁶Konrad J. Demonstration of Tubercle Bacilli in Circulating Blood (Löwenstein Method). Dermat Ztschr 66: 30-37 1933.

tubercle bacilli. The appearing of syphilitic papules in areas of friction and maceration is well known.^{18 19 7}



Fig 1—Trichophyria (Courtesy Division of Dermatology Department of Medicine University of Chicago)

⁷Jadassohn W. Trichophyria. Untersuchung u. über hämatogene traumatisch bedingte Hauttuberkulose Arch f Dermat u Syph 159 3 4-233 1930

Common sites of microbic deposits are the vascular nets which surround the *hair follicles*. Hematogenous follicular rashes (lichen) are well known in mycoses syphilis tuberculosis and other diseases. J. Jadassohn⁸ suggested that the fungi in the blood stream like to settle in the follicles because of the close relation to the hair their preferred medium. Microbic metastases in the capillary loops of the *papillae* may cause scarlatiniform rashes roseoli or papules. Those in the *subcutis* produce nodules of all sizes. The *larger blood vessels* especially in the *subcutis* are another target. Thus reticulated livedo racemosa like forms may ensue as is occasionally seen in syphilis. The *veins* may be the origin of deep nodules in late syphilis. J. Jadassohn⁸ felt that these infections originating in the walls of veins (Wolters⁹) do not stem directly from the blood in the veins but rather from the blood in the *vasa vasorum*. Thus the point of attack contributes to shape the clinical pictures of which lichenoid follicular rashes roseoli and erythema nodosum are the main representatives.

Other Characteristics of Hematogenous Skin Infection—Perhaps even more important than the site of the microbic metastasis is the *allergic response* of the skin. Almost always some allergy has already developed when from the primary focus of infection microbes are disseminated through the circulation. The specific skin reactions are mostly positive. Bloch¹⁷ and other authors have seen fresh crops follow injections of specific allergens. The allergic reactions in hematogenous skin infections may though frequently strong be weak or negative as suggested by the so called *anergic tuberculids*. In other instances of weak allergy the metastatic lesion shows features of a primary infection that is greater abundance of microbes and nonspecific inflammation. Miliary tuberculosis and early syphilis are examples. As the immune biologic reaction grows in strength fewer germs and increasingly tuberculoid histologic structures will be found. This is the case in tuberculosis lichenoides in tuberculoid leprosy in leishmaniasis and especially in the late stages of syphilis. Syphilids are rich in spirochetes when the luetin allergy is lacking and poor when it is present. Not only the skin may have changed its specific reaction since there are many indications that the microbe itself may have become allergic in the course of its contact with the host. For instance spirochetes and other protozoa may become resistant to previously effective drugs.

General *septic symptoms* like malaise chills and fever and swelling of the lymphatic nodes and joints may accompany the crops.¹⁷

The general course of hematogenous infectious skin eruptions is usually benign. There is a marked tendency to spontaneous involution as is the case in some tuberculids.

The *distribution* of hematogenous infectious dermatoses exhibits some characteristic features. One would expect that microbes which invade the blood stream especially the pulmonary veins and the large arteries would land in fairly even distribution in the entire skin. This is not always the case. Syphilitic

⁸Jadassohn J. Hematogenous Infections Diseases of the Skin Arch Dermat & Syph 21 56535 1930

⁹Wolter M. Lupus nodularis hematogenus Ursprungs Arch Dermat & Syph 69 83 1904

roseola the acute exanthems and other blood borne infections in spite of the great number of individual lesions show modifications in their distribution caused by peculiarities of the terrain. Other examples of uneven dissemination are the circumoral pallor in scarlet fever the predilection of the upper half of the body in variola and varicella the often exclusive localization of papulonecrotic tuberculids on the extremities and of some trichophytids on the palms. Of course symmetric dissemination and the appearance in crops as seen in secondary syphilids or in acute exanthems suggest hematogenous infection but asymmetry does not rule it out. The sarcoids and tertiary syphilis are usually asymmetric. Paucity of microbes in the blood stream or paucity of those germs which can succeed in setting up a hematogenous skin infection may explain the lack of symmetry.

Pyogenic Focal Infection—The hematogenous skin infections from streptococcic or staphylococcic foci particularly in the teeth and tonsils have so far not found the same interest among dermatologists as the corresponding manifestations in the other organs among other specialists. It appears that there exist two groups of investigators who do not seem to know much of each other the dermatologists with the microbids on one side and the proponents of the classical focal infection on the other. The former frequently show a skeptical attitude toward the achievements of the latter who in turn often ignore the work of dermatology in this field.*

Both schools struggled with the question of whether toxic products of microbes are able to produce specific dermatomes or whether hematogenous infection with living germs is a necessary prerequisite.

Today the importance of the question has diminished since it is known that toxins from microbes may produce lesions similar to those of living bacteria and that absence of microbes in microscopic and cultural tests does not prove that the questioned lesions are not caused by germs. J. Jadasohn²¹ emphasized on several occasions the clinical similarities of many hematogenous toxic and hematogenous infectious dermatoses. Purpura is an example of a dermatome common in infections as well as in poisonings.

From the pathogenesis of the tuberculids and trichophytids which are more often infectious than toxic and also from other observations we may conclude that the secondary foci are likely to be of a bacteremic and metastatic nature although bacteria are rarely found in the secondary skin lesions.

The last comprehensive review of the field of focal infection by Gutzeit and Parade²² (1939) with a bibliography of about 1700 items does not mention the names of J. Jadasohn or H. Bloch nor those of their pupils. And this is spite of the fact that most of these authors worked for a long time in the same block in the University Hospital in Breslau, Germany.

(Gutzeit H. and Parade C. W. Focal Infect. Ergebn. d. inn. u. Chir. Med. 14: 613-7, 1939.)

²¹Jadasohn J. Hematogen Dermatose. Zbl. 35: 607, 1931.

The conception of focal infection is based on the work of Passler³² Hunter³³ Billings³⁴ and, particularly, Rosenow³⁵ but the older literature also contains much material pointing in the same direction. The term *focal infection* (focus of infection) was coined by Billings³⁴ who defined it as a circumscribed area infected with pathogenic microorganisms and usually communicating with a mucous or cutaneous surface causing secondary foci through various ways especially through the blood stream. Later the definition became more precise. Focal infection may now be defined as a disease caused by a chronic focus of infection which harbors pathogenic microorganisms and though often dormant itself continuously or continually causes remote symptoms (modified after Gutzert and Parade)³⁶ The teeth and the tonsils are the main sites of the primary foci³⁵ followed in frequency by the paranasal sinuses the middle ear the bronchi the uterus and



Fig. 9.—Focal infection. Sudden and often recurrent crops of acute circumscribed erythema of the cheek. Attacks ceased entirely after extirpation of chronically infected appendix.

adnexa the prostate the intestinal tract and some other less common sites like varicous ulcers and bronchiectases. Rosenow³⁵ to give an example found tonsillary foci in 51 per cent of his patients with arthritis and in 74 per cent of those designated as having infective lesions of the skin. In the latter group 77 per cent had infected teeth.

³²Passler H. Ueber die Beziehungen einiger pathologischer Krankheitszustände zu chronischen Infektionen der Mundhöhle. Verhandl. d. deutsch. Gesellsch. f. inn. Med. 26. Kongr. p. 321, 1909.

³³Hunter W. Role of Sepsis and Antisepsis in Medicine. Lancet i 77, 1911.

³⁴Billings W. Focal Infection. Lane Medical Lectures. New York, 1916. D. Appleton & Co.

³⁵Rosenow F. C. Zusammenfassung der Forschungsergebnisse über Lokalfunktion und elektive Lokalisation. Med. Klin. 27, 325, 1931.

³⁶Rödel R. Ueber Fokalfunktion. Verhandl. d. deutsch. Gesellsch. f. inn. Med. Kongr. 51, 455-486, 1930.

³⁷Rosenow E. C. Die Infektion und elektive Lokalisation. Verhandl. d. deutsch. Gesellsch. f. inn. Med. Kongr. 42, 408, 1930.

The bacteria which cause focal infection are predominantly streptococci especially the viridans type although staphylococci *Escherichia coli* gonococci and others also have significance Billings³⁴ and Rosenow³⁵ showed that the streptococci in the living tissue of the primary foci can change their characteristics in various ways There were changes in virulence changes in cultural behavior and even transition into other forms for example from streptococci into pneumococci The observations on character and extent of such mutations are still controversial but the majority of the bacteriologists recognize them in principle The explanations for the emission of bacteria into the circulation in crops have been mentioned in the first half of this chapter The finding of streptococci in the blood³⁶ is relatively infrequent and there are many series of observations with entirely negative results The probability of finding small numbers of bacteria in the blood is small The paucity of germs in the blood distinguishes focal infection from true sepsis It is well that Billings³⁴ changed the misleading term oral sepsis to focal infection

A most controversial subject was and still is Rosenow's³⁷ theory of the *elective localization* of the microbes especially the streptococci Rosenow,³⁷ who considers the assumption of an elective localization as basic in his work showed in a very large series of controlled experiments that streptococci isolated from primary foci had a surprising tendency to produce lesions in animals which corresponded to the secondary lesions seen in the patients from whom the strain was derived Thus for example streptococci isolated from teeth and other primary foci in 1539 cases of ulcers of the stomach and duodenum produced in 65 per cent of the animals which had been infected intravenously comparable stomach or duodenal lesions Other examples of elective localization are the tendency of green producing streptococci to produce lesions in the cardiac valves and of hemolytic streptococci to localize in the joints The percentages in which lesions could be produced in the rabbit were mostly around 60 often higher rarely lower Thus in 60 per cent of nine cases of erythema nodosum and of twenty nine cases of herpes zoster comparable skin lesions were produced in the rabbit These findings were startling The experiments were most expertly executed and the numbers of cases and controls for example 723 cases of arthritis 206 cases of ulcerative colitis were large One would think that Rosenow's³⁷ impressive material should have settled the question of elective localization in a positive sense once and forever However while confirmations were forthcoming³⁸ many investigators among them men who had been trained by Rosenow failed to corroborate his results or obtained smaller percentages³⁹ Particular care was taken by Von Albertini and Grumbach⁴⁰ These authors could find no definite proof for the existence of an organotropism of the streptococci They believe that the individual resistance of the animals and not the selective organotropism of the microbes decides whether a localized abscess or a generalized sepsis will follow the injection of

³⁴ Haden R L and Jordan W H Multiple Onychia as a Manifestation of Focal Infection Arch Internat & Syph 31 36 1933

³⁵ Azzi Azzi Focal Infection Schweiz med Wchnschr 71 1365-1366 1941

³⁶ Von Albertini A and Grumbach A Focal Infection Schweiz med Wchnschr 68 1309 1938

cultures. The authors emphasize the fallacies resulting from comparing secondary lesions in an animal which had not been infected before and which receives a single massive dose of bacteria with secondary infection in man where the dissemination of microbes probably occurs continually and allergy has had a chance to develop. Von Albertini and Grumbach's⁴⁰ experiments did not deal with skin diseases. The role of specific *allergy* in streptococcal infections has been demonstrated and emphasized by many observers. In proper concentration skin tests with autogenous vaccine can be made and therapeutic effects reached. Humoral antibodies have been demonstrated. However agglutination precipitation and other tests with hyperimmune sera which had proved of great value in Rosenow's hands have not been found suitable by other authors because of the pronounced tendency of the streptococci to spontaneous agglutination.⁴⁰ Intercurrent infections climate menstruation nutrition endocrine and other factors may also modify the allergic reactions.

Diagnosis—Many authors stress the importance of a history of frequent colds recurring tonsillitis,² postnasal dripping occasional stiff neck myositis arthritis transitory tenderness in various joints neuritis endocarditis appendectomy and other episodes of pyogenic infections. Of course the history only suggests focal infection and it constitutes good grounds for a careful investigation.⁴⁰

The collaboration of dentists rhinologists and radiologists is often needed. Specimens for culture should be taken from the depth not from the surface. This is especially important with regard to the tonsils and the teeth. The most suitable medium for cultures seems to be Rosenow's brain broth. From the isolated strains a vaccine may be made and intracutaneous skin tests done. These tests are difficult to interpret and controls are necessary. Various laboratory methods to demonstrate humoral antibodies are used by some authors but they have not gained general acceptance.⁴¹ The demonstration of an infectious focus does not prove that the dermatosis in question is caused by the focus.

The hematologic methods as well as exact thermometry may give hints with regard to the existence of an infection. Gutzeit and Kuchlin⁴² determine the blood sedimentation rate and expose the area suspected of an active focus to ultra short waves. An exposure of seven minutes is used for teeth and twelve minutes for the tonsils. An increase of the sedimentation rate two to four hours after the provocation is supposed to indicate activity of the focus in question. The patient should be fasting. The value of the method is still controversial since other authors obtained similar reactions from normal teeth. The advantage of the test is that it is based on the objective phenomenon of the sedimentation rate and not on more or less vague exacerbations of pain or other sensations. It seems that no absolutely reliable test for the activity of a focus has been devised.

⁴¹ Ayres S. Jr. and Anderson N. P. Focal Infection in Dermatology. Arch. Derm. & Syph. 421-431 1936.

⁴² Gutzeit K. and Kuchlin W. Beitrag zur dentalen Infektion und ein neuer Weg in ihrer Diagnosestellung durch kurzweilige Provokation. München. med. Wchnschr. 84 961-965 1937.

Treatment—So far the best evidence to prove the causal relationship between a lesion in the skin (or elsewhere) and a focus of infection is the therapeutic effect of the elimination of the alleged focus. But even here great skepticism is necessary to prevent post hoc ergo propter hoc conclusions since many of the conditions in question for example rosacea eczema and lichen planus take an irregular course with frequent remissions and exacerbations. Penicillin and the sulfonamides are the first drugs to be tried. The eradication of dental tonsillar and other foci by surgical means should be attempted. The removal of one accessible focus does not rule out the existence of other inaccessible or undetected foci. Some foci like endocarditic or aortic granulations are beyond the surgical reach or would involve formidable operations which are not warranted. Conservative topical methods include local disinfectant and cleansing procedures like swabbing and gargling but they will hardly influence encapsulated foci in the depths of tonsillary crypts. The treatment with autovaccine from the recovered strains should be tried but many authors are skeptical. Ayres Jr and Anderson⁴¹ recommend gradually increasing intravenous injections of the vaccine. Nonspecific protein injections may be tried cautiously but there is some danger of producing reactions in hyperergic patients. General procedures like the salt free diet of Gerson Sauerbruch, and Hermann dorfer hydrotherapy and ultraviolet light have been recommended. Acute exacerbations following such apparently harmless treatments as mud baths are known. Severe exacerbations have been observed occasionally after surgical treatment of foci for example arthritic exacerbation following extraction of infected teeth or new crops of gonorrheic keratoses after dilatation of a urethral stricture.⁴² Ayres Jr and Anderson⁴¹ give a long list of dermatoses suspected to be caused by focal infection. Most of the alleged conditions bear remarks like some cases or occasionally intimating how little solid ground the imposing work has yielded for dermatology. In the following list which is in part after Ayres Jr and Anderson⁴¹ the dermatoses are grouped according to the validity of the arguments claiming focal infection in their pathogenesis.

GROUP I

The nature of the dermatosis as a hematogenous infection or toxic manifestation is well established in

- Syphilis
- Leprosy
- Tuberculosis
- Acute exanthems
- Septic pyemias
- Erythema nodosum
- Trichophytids and other mycoses for example in blastomycosis
- Tularemia
- Keratoderma bi hemorrhagicum
- Typhoid fever
- Acute exanthematous diseases and many other rashes in infections

⁴¹Ayres Jr M Relationship of Arthritis to Oral Diagnosis III focalisation and Streptococcus Vaccine Therapy Am J O rhodontics 27 149-156 1941

GROUP II

Focal infection has been shown or suggested with more or less good reasons in some cases of

Acne rosacea^{44 46}
 Herpes zoster^{31 35 45}
 Erythema elevatum diutinum⁴⁶
 Lupus erythematosus acutus disseminatus⁷
 Generalized telangiectasis^{48 49}
 Acrodermatitis continua⁵⁰
 Angioneurotic edema and urticaria⁵¹
 Alopecia areata⁴⁵
 Acne vulgaris (some cases of severe involvement)^{32 43}
 Dermatitis herpetiformis^{52 54}
 Pemphigus⁵⁴
 Nonmycotic vesicular eruptions of the hands and feet
 Purpura
 Sycosis vulgaris
 Eczema^{22 31 48 53}
 Dyshidrosis⁵⁵
 Lichen chronicus simplex⁴²
 Chronic paronychia⁸
 Pyodermic ulcerations in chronic ulcerative colitis⁵⁶
 Erythemas of various kind⁵
 Lichen planus⁵⁶

- ⁴⁴Feit H, La slo E A and Vero F Rosacea as a Bacterial From Focal Infection J A M A 105 1738 1935
- ⁴⁵Barber H W Dental Infection and Disease of the Skin Proc Roy Soc Med 20 39-48 1927
- ⁴⁶Weldman I D and B sançon J H Erythema elevatum diutinum Arch Dermat & Syph 20 593 19 9
- ⁴⁷Madden J F Acute Disseminated Lupus Erythematosus Arch Dermat & Syph 25 854 1932
- ⁴⁸Ayres S Jr Burrows L A and Anderson N I Generalized Telangiectasia and Sinus Infection Arch Dermat & Syph 25 56 1932
- ⁴⁹Becker G W Generalized Telangiectasia Arch Dermat & Syph 14 387 19 6
- ⁵⁰Barber H W and Eyre J W H Acrodermatitis continua (Hallopeau) or Dermatitis Repens (Crocker) Brit J Dermat 20 485 1927
- ⁵¹Samson H C Some Cutaneous Effect of Dental Septic Lancet 202 889 891 1927
- ⁵²Richter W Focal Infection Dermat Wehnschr 109 911 915 1939
- ⁵³Junstlin W Dentaler Fokus und Hautkrankheiten in Tübingen Dissertation 1937
- ⁵⁴Welsh H L Specificity of a Streptococcus Isolated From Patients With Pemphigus Arch Dermat & Syph 20 611 1934
- ⁵⁵Isher J W Focal Infections in the Etiology of Eczema Am J Med 170 7 3 7 7 19 5
- ⁵⁶Gomes A A Eczema and Dental Disease Brit Med J 2 590 19 6
- ⁵⁷Miemmesheim R A M Fokale Infektion und chronisches Ekzem Arch f Dermat u Syph 157 183 195 19 0
- ⁵⁸Kémerli H Ursachen d Dyshydrosis und Ekzeme Dermat Wehnschr 91 1615 1619 1930
- ⁵⁹Jankelson I R and Nas H B F Pyogenic Skin Lesions Accompanying Chronic Ulcerative Colitis Am J Dig & Nutrition 3 19 1936
- ⁶⁰Robert H L Focal Infection Brit J Dermat 33 319 334 3 3 373 1921

CHAPTER II

SYSTEMIC INFECTIONS

Pyogenic Septicemia

Bacteremia does not necessarily produce clinical symptoms. If the microbes enter the blood stream in small numbers or only once the natural bactericidal power of the blood often disposes of them quickly as illustrated by postoperative bacteremia. If the blood is repeatedly or constantly fed with microbes from a focus of infection such syndromes as discussed under tuberculosis, gonorrhea or focal infection may ensue. The massive presence of bacteria in the blood together with the outstanding clinical symptoms of characteristic fever or wasting is called septicemia or sepsis. If the development of multiple abscesses is an outstanding feature as is often seen in staphylococcic septicemia the term pyemia is often used. The term toxemia should be reserved for those conditions which are caused by bacterial toxins such as diphtheria, tetanus and botulism.

The bacteria causing sepsis in two series of 150 and 255 cases¹ were found to be *Staphylococcus aureus* in 36.5 per cent, *Streptococcus hemolyticus* in 36 per cent and various types of pneumococci in 5.5 per cent. The rest of the list predominantly contains other types of staphylococci, streptococci and the Friedlander bacillus. In other large series the staphylococcic cases outnumber the streptococcic cases 2:1 or 3:1.²

Otitis, carbuncles and related conditions are listed (20 per cent)³ as the most common source of sepsis, others being operation (14 per cent), infections of the genitourinary tract (9 per cent), paranasal sinuses (6 per cent), liver and gall bladder (4 per cent) and miscellaneous (19 per cent). The onset is often sudden, occasionally with a severe chill and fever. Chills and spiking temperatures occur in about one half of the cases. Sustained low fevers are common and seem to entail a higher mortality.⁴ Usually the bacteria can be isolated from the blood. Endocarditis and metastatic abscesses are the most characteristic complications and causes of death.

Hemolysis, hemoglobin staining of the lining of the blood vessels, abscesses, particularly of the lungs, reddened and hypertrophic bone marrow, cloudy swelling of the kidneys, liver and heart and a moderately enlarged and very soft spleen are the ordinary post mortem findings.

Since the introduction of the sulfonamides the mortality rate has dropped from 67 to 54.5 per cent⁵ in staphylococcic septicemia alone from 82 to 74 per cent.⁶ The advent of penicillin has probably reduced the mortality still further.

¹Neuhof H. and Aufse A. H. Pyogenic Sepsis. 255 Cases. Surg., Gynec. & Obst. 77: 544-552, 1943.

²Mendell T. H. Staphylococcic Septicemia. 35 Cases. Arch. Int. Med. 63: 1008-83, 1939.

³Skinner D. and Keefe E. C. Significance of Bacteremia. Arch. Int. Med. 88: 851-875, 1941.

Dermadromes—In contrast to the importance of the skin as a cause the dermadromes of septicemia are neither very common nor important compared with the severity of the general septic syndrome. There seem to be some distinguishing features between the staphylogenic and streptogenic hematogenous skin lesions (pyemids) ^{64 65}

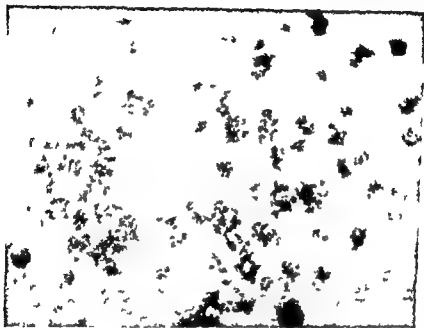


Fig 3—Acute streptogenic septicemia. Large skin eruption of grouped follicular hemorrhagic lesions. Back.

Staphylogenic Pyemids—Pyemids occur in about one third of the cases of staphylogenic sepsis ^{66 67}. They are probably more common than those caused by streptococci ⁶⁷. They appear suddenly, often with chills and fever heralding a turn for the worse ⁶⁸. They often start with rashes consisting of macular or urticarial lesions, vesicles, umbilicated pustules, or bullae ⁶⁹. The tendency to epidermolysis is considered by some authors a characteristic but inconstant ⁶⁴ feature of staphylogenic pyemids ⁷⁰. Petechiae are seldom absent ⁷⁰. Metastatic subcutaneous nodules and abscesses in varying sizes and depths may, especially in infants, give the impression of furunculosis ⁷¹. Mendell ⁶² saw metastatic ab-

⁶⁴Fuchs D. Pyämische Dermatiden (Pyämide). Handb d H u Gk 9 2 440-472 1934

⁶⁵Robinson S. Septicemia Eruptions. Jrol & Cutan Rev 41 490-497 1957

⁶⁶Fejenthal W. Über Staphylokokkensepsis. Mitt d Grenzgeb d Med u Chir 42 18 262 1930

⁶⁷Franke J. Metastatische Dermatosen bei akuten bakteriellen Allgemeinerkrankungen. Arch f Dermat u Syph 129 386-403 1950

⁶⁸Corke P and Grolfe H. À propos des faits nouveaux de staphylococcémie. Presse Méd 34 611 1956

⁶⁹Strandberg J. Ein Fall von vesicopustulösem Pyämide. Arch f Dermat u Syph 121 85 1910

⁷⁰Davis T H. Septicemia. Practitioner 137 545-57 1945

⁷¹Pfinger E. Dermatide pyämica. Wien klin Wchnschr 9 547-548 1896

scabs in the skin occur in 30 per cent of thirty five cases of staphylogenic septicaemia. Nodules which do not form abscesses may resemble erythema nodosum⁷ (McCrea after M. Barber³).



Fig. 4.—Erythema due to staphylogenic septicaemia after furuncle. Erythema and scaling.



Fig. 5.—Cutaneous staphylogenic septicaemia. Erythematous eruption.

Erythemas of varying shape and extent, sometimes clinically identical with true scarlet fever,⁸ sometimes roseolar or exudativomultiform^{7,9} (Bloemen and Scalognie³) but also papules, vesicles, pustules, nodules, and petechiae may be seen simultaneously. Ulcerations are rare.

Barber M. Staphylococcus Albus Septicaemia. Brit. M. J. 2: 40, 409, 1921.
 Dohm H. A. Scarlatiniform Exanthem in Infections With Staphylococcus Aureus Hemolyticus.
 Klin. W. hnschr. 17: 1649, 1691, 1935.
⁸Bloemen J. J. and Scalognie H. W. M. In: Atlas of staphylogenic dermatoses. Dermat.
 Wehseh. 110: 477, 1940.

The histologic findings are in line with the clinical picture. Edema and vesicles of the epidermis, milium abscesses and papillary capillaries stuffed with cocci and surrounded by leukocytes are the dominant features.

Streptogenic Pyemids—Pyemids are reported to occur earlier in the course of streptogenic septicemia than the corresponding staphylogenic eruptions. They also often start as macular, sometimes morbilliform or scarlatiniform exanthems, sometimes as less numerous or solitary erysipeloid patches⁶⁷ (Werther and others after Fuchs⁶⁶). Papular and papulopustular⁷⁵ or bullous eruptions⁷⁶ are not rare. Most authors emphasize the hemorrhagic tendency of the streptogenic eruptions. Petechiae, especially on the lower legs, on the buccal mucosa and on other sites are common. They may become vesicular or bullous. In the mouth, small yellow specks may be seen on the petechiae.⁷⁹ Erythema nodosum,⁷⁷ erythema multiforme⁸⁰ and local gangrene and ulceration have been described, although the tendency to suppuration is much less pronounced than in staphylogenic lesions. Microscopic examination reveals dense streptococcal emboli in the small vessels, particularly in the vasa vasorum,⁷¹ surrounded by leukocytic infiltrations. The damage to the vascular wall is demonstrated by the extravasation of red cells together with cocci.

Sabouraud (Kitchevatz⁷⁸) is reported to have postulated a staphylostreptogenic dermatosis analogous to the trichophytids and epidermophytids. Of course, he meant a hemogenous infection originating from a pyoderma and not from septicemia, which in his days was already well known. A lichen pyodermicus after widespread pyoderma, formed by acuminate micropapules⁷⁹ and resembling lichen trichophyticus or lichen scrophulosorum, and also other benign pyodermids, have been described under various names, although general recognition is still lacking.

It is true that within certain limits the various microbids resemble each other. M. Favre⁸⁰ observed in patients with furuncles and impetigo, lichenoid lesions and squamous seborrheic plaques, sometimes resembling pityriasis rosea. The author saw, in a case of acute pustular acne vulgaris, superficial pink lesions which at their edges consisted of very small, dull papules. These lesions disappeared when the acne eruption quieted down. A series of thirty cases of streptostaphylotoxids, the largest so far, was presented by Kitchevatz.⁷⁸ He too saw pyodermids after widespread streptoderma or deep ulcerating staphylodermas. The streptopyodermids, which often originate from rhagades behind the ear, itched more and were about five times as common as the staphylopyodermids. Kitchevatz⁷⁸ saw erythematous spots which resembled syphilitic roseola, scarlatiniform or lichenoid rashes, vesicular, papular and erysipelatous.

⁶⁷Nicolas J. Mouton, H. and Caté J. Septicopybémie streptococcique avec éruption pemphigolide. *Province méd. Paris* 31: 101-103, 1913, abstracted in *Dermat. Wechnsch.* 58: 131, 1914.

⁷⁵Biber, I. in H. and Fischer, M. *Fim Erythema nodosum—ähnlich u. gutartig verlaufend*. *Pyämid Arch. f. Dermat. u. Syph.* 149: 57, 1925.

⁷⁶Kitchevatz, M. *Strepto-staphylococcus cutaneus*. Intern. Derm. Congr. Copenhagen, 1930.

⁷⁷Schreus, H. T. and Coehl, F. Lichenoid Eruptionen I. *Pyodermiden* (Lichen pyodermicus). Bemerkungen über Komplementablankung im Blute II. *Staphylokokken und Trichophytenkrankungen*. Wirkung d. röntgenstrahlen. *Dermat. Ztschr.* 31: 273-31, 1910.

⁸⁰Favre, M. Angiodermite pigmentée et purpurique. *Nouvelle pratique dermatologique*. Vol. V. Paris, 1936. *Nia. on & Cl.* pp. 413-430.

lesions and erythematous and herpetiform enanthemas. There were also focal reactions and the appearance of new lesions after autogenous vaccines and toxins. This relatively large amount of material has not found much attention. Occasionally benign pyoderms,⁴¹ circinary or annular erythemas⁴² and acne necrotica resembling embolic infarctions have been recorded after various primary pyogenic infections. Balog⁴³ saw primary staphylogenic skin infections followed by disseminated semiglobular later umbilicated papulopustules which appeared in crops and subsided with the cure of the primary focus. The embolic bacterial character of these benign pyemids could be demonstrated. More corroboration is needed, however. The same is true of the claims⁴⁴ that various types of eczema among them nummular eczema, are secondary pyoderms and that nonmycotic pustular eruptions of the hands and feet are pyoderms.⁴⁵

In the treatment of all pyemids penicillin must be tried first.

Subacute Bacterial Endocarditis, Endocarditis Lenta (Jaccoud Osler's Disease)

The streptococcus viridans which is the most common cause of subacute bacterial endocarditis probably stems from focal infections of the teeth, paranasal sinuses and tonsils.⁴⁶ The streptococci produce vegetations on the heart valves especially in patients with congenital or rheumatic heart disease. The vegetations cause fever, bacteremia, myocarditis, glomerulonephritis and embolic metastases. There is a great variety of nervous, hematologic and other symptoms. The onset is gradual. After an early nondescript subfebrile stage of increasing malaise the disease develops into a severe illness with many septic complications and ends fatally after several months in over 90 per cent of the cases. A small minority reaches a bacteria free nonactive stage which too terminates fatally from valvular disease and cardiac decompensation.⁴⁷ Penicillin in high doses over many weeks seems to be effective.^{48a}

Dermadromes—About one third of the sufferers from subacute bacterial endocarditis are anemic and very pale and later jaundiced (90 per cent).⁴⁹ Sweating is an annoying symptom. Petechiae well known to occur in other streptococcal infections are common. In an analysis of eighty eight cases they were found in the skin in 60 per cent,⁵⁰ in the mucosae in 14 per cent and in the retina in 11 per cent. The petechiae appear in crops and sometimes have pale yellow or necrotic centers.^{51 52} Petechiae under the nails are stretched to

⁴¹Bošnjakovi S. Several Forms of Chronic Pyoderma. Lij. čn. vj. s. 54. 261-67. 1932. Zbl. 62. 62.

⁴²Balog F. Benign Embolic Pyemid. J. Invest. Dermat. 5. 107. 1940.

⁴³Krzyżakowski F. Pczema From Pyogenic Infection. Izszeg. dermat. 24. 208-24. 1939. Zbl. 91. 1030.

⁴⁴Andrews G. C. and Wachacek G. F. Postular Bacterids of the Hands and Feet. Arch. Dermat. & Syph. 32. 637-64. 1935.

⁴⁵Oler W. and Christman H. A. Principles and Practice of Medicine. ed. 15. New York. 1944. H. Appleton Century Company, Inc.

⁴⁶Fleming A. Penicillin Its Practical Application. Philadelphia. 1946. The Blakiston Co.

⁴⁷Middleton W. C. and Burke N. St. aptococcus Viridans Endocarditis Lenta. Am. J. M. Sc. 198. 301-3. 1939.

⁴⁸Guldburg F. Dermatoses in Endocarditis. Venereol. 8. 51-53. 1931. Zbl. 41. 111.



Fig 6—Acute bacterial endocarditis, purpura



Fig 7—Subacute bacterial endocarditis, purpuric rash

short lines by the growing nail and are often called *splinter hemorrhages*. Petechiae about the nails resemble paronychia but they fail to come to a head⁸⁸. If they have central blisters they resemble erythema multiforme⁸⁹. Other varieties of these eruptions have been described as papular or lichenoid⁹⁰ maculo

⁸⁸Eichbach H. Éruption cutanée et endocardite infectieuse prolongée. Bull et mém Soc méd d'hôp de Paris 54: 97-299, 1930.

⁸⁹Gottlieb M. Manifestations cutanées dans l'endocardite lente. Zbl 25: 43, 1931.

⁹⁰Weissenbach R, J. Martineau J and Brisot J P. Manifestations cutanées de la maladie de Jaccoud Osler. Bull Soc Française de dermat et syph 29: 1688-1701, 1933.

papular and purpuric⁴¹ or subcutaneous and nodular (Osler's nodes). They sometimes prefer the extensor surfaces sometimes the palms and soles (Janeway lesions).

These eruptions heal spontaneously. Petechiae on the rectal or sigmoid mucosa are supposed to be an early diagnostic sign in subacute bacterial endocarditis.⁹

Rheumatic Fever

Rheumatic fever⁴²⁻⁴⁴ is an infection probably caused by hemolytic streptococci. Hereditary and constitutional factors as well as exogenous factors like exposure to cold damp climate and youthful age, favor the infection. The outbreak often starts with pharyngitis tonsillitis and tender joints. Chills usher in the fever which is high but does not follow as regular a pattern as in



Fig. 8.—Rheumatic nodules.

scarlet fever. Acute arthritis involving one joint after the other is the center of the clinical picture. Endocarditis, anemia and more rarely pleurisy, iritis, chorea and encephalitis may appear. While the mortality in the early stages does not exceed 3 per cent,⁴⁵ the frequent cardiac damage plays an important part in the mortality in later life.

The pathologic findings are characterized by small widespread circumscribed granulomatous nodules which are most often found in the ventricular walls of the heart (Aschoff bodies) and in the walls of many arteries especially of the aorta and the coronary and in the pericardial tissues.

⁴¹Lihman F. and Sack B. A Hitherto Undescribed Form of Valvular and mural Endocarditis. Arch. Int. Med. 33: 701, 1918.

⁴²Felton J. Intestinal Petechiae as Diagnostic Sign in Subacute Endocarditis. Internat. Clin. 2: 57-67, 1941.

⁴³Leichtentritt B. Acute Articular Rheumatism. In Pfaunder and Schlossmann. Diseases of Children. Vol. III. Philadelphia, 1934. J. B. Lippincott Company. pp. 357-375.

⁴⁴Leichtentritt B. Die rheumatische Infektion im Kindesalter. Ergebn. inn. Med. u. Kinderh. 37: 1-99, 1930.

Dermadromes—The skin participates in the syndrome in various ways. *Pallor* is common. The skin of the extremities frequently becomes glossy and there may be redness of the palmar eminences. The palms are moist. The repeated *sweating* often causes miliaria especially on the chest and the inner surfaces of the arms. *Pelechiae* and other hemorrhagic signs have often been observed. Keil⁹⁵ saw them in 10 per cent of 523 cases. Recently⁹⁶ it has been demonstrated that children with rheumatic fever generally show a low capillary resistance especially in late winter and before barometric depressions.



Fig. 9.—Cutan subcutaneous rheumatic nodules about the olecranon.

Urticaria occurs in the early stages.⁹⁷ *Erythema nodosum* has often been linked to acute articular rheumatism^{98, 101} but the evidence is scant and there is a modern tendency to deny any relationship.⁹⁹ The observation that such recognized rheumatic diseases as endocarditis and chorea are seldom connected with erythema nodosum has been interpreted as evidence against its rheumatic character¹⁰⁰ (Kassowitz after Leichtentritt⁹⁹).

⁹⁵Keil H. Rheumatic Erythema. *Ann Int Med* 11: 2246, 1939.

⁹⁶Brown E. L. and Watson V. P. Capillary Resistance in Rheumatic Children. *J. Pediat* 18: 3: 8-336, 1941.

⁹⁷Traub-Frich. Ueber die Bedeutung der Hauterscheinungen beim akuten Gelenkrheumatismus. *Ztschr. f. Klin. rh.* 88: 769-789, 1937.

⁹⁸Milady H. G. Dermatoses of Rheumatic Fever. *Urol. & Cutan. Rev.* 45: 713-714, 1941.

⁹⁹Keil H. Relation of Erythema Nodosum and Rheumatic Fever. *Ann Int Med* 11: 1686, 1937.

¹⁰⁰Peet F. Zur Ätiologie des Erythema nodosum. *Schweiz. med. Wchnschr.* 11: 68, 685, 1916.

Erythema multiforme^{101 104} sometimes appears with exacerbations of the articular disease

The erythemas in rheumatic fever seem to have been over classified from a morphological viewpoint. It is sufficient to distinguish between nodular papular and erythematous rheumatic skin manifestations. Transitional forms exist. Keil⁹⁵ found 181 eruptions among 523 cases of rheumatic disease. Besides more or less nonspecific dermatoses like hemorrhagic eruptions, telangiectases, urticaria, scarlatiniform exanthems in approximately 10 per cent of the cases, rheumatic erythemas and in 7 per cent subcutaneous nodules could be found. *Erythema nodosum* is not included.



Fig. 10.—Cutaneous rheumatic nodules. (From Rosenberg W. A. Arch. Dermat. 1934.)

The *rheumatic nodules* (*rheumatismus nodosus*) appear in crops more often in the subcutaneous tissues than in the cutis itself.¹⁰⁵ They vary from mustard seed to olive size. They are movable, nontender, and covered with normal skin. They are most often found over the olecranon, about the elbow joint, over the knuckles and other bony eminences, for example, over the forehead and along the crest of the vertebrae. The nodules are often symmetrically distributed, particularly on the limbs. The rheumatic nodules must be regarded as indicating activity of the rheumatic infection, which means an unfavorable prognosis.^{106 108} Other rheumatic lesions, especially rheumatic heart disease, are almost always

¹⁰¹Jaeger G. Die Hautveränderungen bei dem akuten Gelenkrheumatismus nebst Bemerkungen über Erythema multiforme. Wien klin. Wchnschr. 10: 841-844, 1897.

¹⁰²Müller Theodor. Ein erythematöses bullöso-pustulöses Exanthem bei Polyarthriti acuta. Dermat. Ztschr. 62: 269-274, 1931.

¹⁰³Mejer August. Akuter Gelenkrheumatismus mit Erythema pustulosum. Ztschr. f. klin. Med. 117: 413-44, 1931.

¹⁰⁴Riehon J., Girard J. and Picard H. Un cas d'érythème multiforme au cours de la maladie de Douglaud. Bull. Soc. franc. de dermat. et syph. (Réunion dermat. Nancy) 45: 1760-1763, 1933.

¹⁰⁵Rosenberg W. A. Cutaneous Rheumatic Nodules. Arch. Dermat. & Syph. 30: 377-384, 1934.

¹⁰⁶Quirke R. R. and Bacal H. L. Significance of Rheumatic Nodules in Childhood. Canad. M. A. J. 46: 370-391, 1941.

present and the mortality is as high as 31 per cent¹⁰⁷ Recently less pessimistic opinion on the prognostic significance of the rheumatic nodules have been voiced¹⁰⁸ It has even been said that the appearance of rheumatic nodules may indicate the subsiding of the particular rheumatic incident though not of the disease¹⁰⁶ Histologically they correspond to the Aschoff nodules of the myocardium Leichtentritt⁹⁴ succeeded twice in isolating streptococcus viridans from excised nodules In a third case he and Biberstein⁹⁴ found cocci in microscopic sections

The rheumatic nodules must be interpreted as true infectious metastases The rheumatic nodules usually heal occasionally they may take on the appearance of chronic hard almond sized subcutaneous cystic tumors in the neighborhood of the large joints especially the elbow Such nodosities which are well known in other infectious diseases particularly spirochetoses are called juxta articular nodules^{109 110 111} H Hoffmann¹¹⁰ however in his comprehensive monograph on juxta articular nodes does not believe that rheumatic fever plays a part in the etiology of these lesions

Cutaneous rheumatic nodules¹⁰ are much rarer than subcutaneous ones They have been observed on the fingers and palms as red not painful slightly indistinct papular lesions which do not ulcerate They consist of perivascular infiltration with endothelial proliferation In later stages giant cells develop¹¹²

Rheumatic papular erythema is a discrete red eruption of small papules mainly but not exclusively about the articulations Keil⁹ found it in 3 per cent of his 523 patients with rheumatic fever Like other rheumatic eruptions it appears in crops Keil⁹ separates erythema marginatum with polycyclic and raised borders from papular erythema Much more significant and better known than the papular eruptions is the flat *annular erythema*¹¹³ which is so characteristic and so intimately connected with rheumatic infection that it can be called a specific rheumatic dermatosis The incidence given by various authors varies widely Erythema annulare is still considered a rare complication which seldom occurs more frequently than in 10 per cent of children with rheumatic fever⁹⁷ (Wallgren after Traub⁹⁷) although Leichtentritt⁹⁴ and Lehdorff and Leiner¹¹³ give figures higher than 60 per cent These differences may be largely caused by the type of clinical material because erythema annulare is mainly a dermatome of rheumatic disease in children with endocarditis The rash starts with pale bluish pink maculae of only a few millimeters in diameter These spots soon blanch in the center and spread peripherally with an active but not infiltrated margin Thus polycyclic or zigzag often rather than almost linear figures result

¹⁰⁷Hayes R M and Gibson S Rheumatic Nodules in Children J A M A 119 554 555 1912

¹⁰⁸McCulloch H in Discussion of Struthers R R and Bacal H L Rheumatic Infection in Childhood Sedimentation Rate and Schilling Count Am J Dis Child 62 1031 1936

¹⁰⁹Horklin H H Subcutaneous Nodules of the Juxta Articular Type Bull John Hopkins Ho 49 5-16 1931

¹¹⁰Hoffmann H Ju taartikuläre Knoten Handb d H u Ch II 1 419-498 193

¹¹¹Katz C Juxta articulaire Knoten bei Gelenkrheumatismus Ztschr f Klin Med 129 363 1936

¹¹²Gadrat J Rheumatismal Papulous Erythema Dermal Lesion of Aschoff Klingen Nodule Type Case Bull Soc franç d dermat et syph 41 178 1788 1931

¹¹³Lehdorff H and Leiner C Erythema annulare Ein typischer Exanthem bei Endokarditis Ztschr f Klin Med 32 46 53 1907

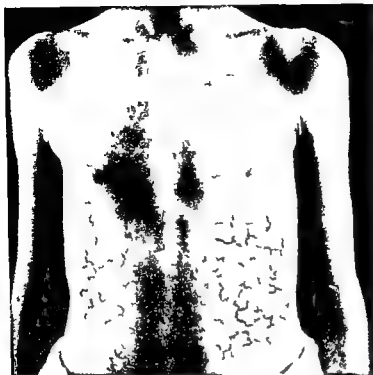


Fig. 11.—Erythema annulare rheumaticum. (Courtesy Dr. Arthur F. Abt.)



Fig. 12.—Erythema annulare rheumaticum. (Courtesy Dr. Erich Urbach.)

The lesions which appear most often on the chest less often on the abdomen back and extensor surfaces of the limbs are delicate not infiltrated not scaly not tender and do not itch. The erythema has not been observed on the mucous membranes. It appears in one or several crops, and the individual crops usually last two to five days.⁹³

Since the eruptions may follow each other in short intervals the patient may have erythema for years. The rash may easily be overlooked. Leichtentritt⁹⁴ found erythema annulare always connected with rheumatic endocarditis or chorea and he emphasizes its ominous significance. Other authors do not share his pessimistic interpretation^{97 114} but all agree that it has not been seen in endocarditis of nonrheumatic character.

The biopsy¹¹⁵ shows neutrophilic infiltration as a main characteristic. Bacteria have not been found in the lesions. Lowenstein¹¹⁶ and his group were able to cultivate the tubercle bacillus from the blood of one case of rheumatic fever with erythema annulare. This finding still lacks confirmation. The eruption is now regarded as an expression of cutaneous allergy.¹¹⁷

Still's disease is a chronic articular disease of childhood. Fever generalized lymphadenitis and splenic tumor are outstanding features. *Streptococcus viridans* has been demonstrated in the blood by Leichtentritt.⁹⁴ Periarticular papules and erythematous eruptions have been reported.¹¹⁸

Palindromic rheumatism is a disease characterized by often recurring relatively short attacks of arthritis.¹¹⁹ Although there is no connection with rheumatic fever intracutaneous and subcutaneous nodules mainly on the fingers have been described in some cases. The nodules were mostly short lived rarely persisting over a long period.

Periarteritis Nodosa

Periarteritis nodosa¹²⁰ is characterized by multiple inflammatory destructive foci in the walls of the smaller arteries which may lead to aneurysm and other severe circulatory disturbances. The clinical picture varies according to the area which is predominantly involved. Males outnumber females 3:1.¹²⁰ Age is not a decisive factor. Acute infectious diseases of many kinds have often been observed to precede the outbreak of periarteritis nodosa. The onset is usually though not always rapid. Repeated attacks and exacerbations often characterize

¹¹⁴Abt A. Erythema Annulare Rheumaticum. Am J M 90 824 1935.

¹¹⁵Carol W. L. L. and Van Krieken J. A. Histopathologie des Erythema annulare von Lehnndorff und Leiner. Acta paediat 17 372 1935.

¹¹⁶Lowenstein Ernst. Die Tuberkelbazillämie in ihrer Auswirkung auf die Gesamtmedizin. Mit einem klinischen Teil von Carl Reitter. Wilhelm Neumann und Otto Kren. Leipzig und Wien 1936. Franz Deuticke.

¹¹⁷Urbach E. and Bleier A. Erythema Annulare Rheumaticum (Lehnndorff Leiner). Ca 9 Arch Dermat & Syph 41 515 5 1940.

¹¹⁸Hench P. and Rosenberg E. F. Palindromic Rheumatism. Proc Staff Meet Mayo Clin 16 808-815 1941.

¹¹⁹Kussmaul A. and Maler R. Ueber eine bisher nicht beschriebene eigentümliche Arterienkrankung (Periarteritis nodosa) die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung inhergeht. Deutsches Arch f klin Med 2 484 1866.

¹²⁰Harris A. W. Lynch C. W. and O'Hare J. P. Periarteritis Nodosa. Arch Int Med 63 1163 118 1939.

the course. In more than 90 per cent of the cases the outcome is fatal after less than one year. In a review of 101 pathologically confirmed cases Harris, Lynch and O'Hare¹⁰ listed as significant symptoms and signs: fever (80 per cent), leukopenia up to 5,400 (70 per cent), renal manifestations like albuminuria (64 per cent), abdominal pain (27 per cent), cylindruria (46 per cent), hypertension (64 per cent), edema (52 per cent, mostly of cardiac distribution), loss of weight, hematuria and neuritis. Thoracic pain, dyspnea, headache and vertigo are common. The diagnosis is usually made post mortem. However, with better knowledge of the dermatomes and greater number of biopsies the disease is being recognized more frequently during life.^{10,11,12}

The cause of the disease is not known but it has nothing to do with syphilis as was early suggested. It is striking that periarteritis nodosa has so often developed shortly after or even in immediate connection with various infectious diseases, especially those caused by hemolytic streptococci. While the staphylococcus, the meningococcus and the gonococcus are on the list of bacteria which have been found in close association with periarteritis nodosa,¹³ the streptococcus is by far the most frequent one. A correlation to rheumatic fever, with Aschoff bodies and verrucous endocarditis, was discovered in four of Spiegel's¹⁴ seventeen cases and in one of Rothstein and Welt's.¹⁵ The clinical course often suggests septicemia. The coincidence with well established allergic states and also experimental evidence of infection¹⁶ suggests allergy as an important pathogenic factor in periarteritis nodosa.¹⁵

The treatment is symptomatic. In one case sulfapyridine together with acetylcholine seemed to be curative.¹⁷

Dermatomes—Cutaneous manifestations occur in about 25 per cent.^{1,3,18} In rare instances almost exclusive involvement of the skin without participation of the internal organs has been observed.^{19,20} The case material permits a tentative grouping^{1,4,16} into nodular erythematous and hemorrhagic eruptions.

The most characteristic element is the periarteritic *nodule* which may be found in or under the skin. These nodules have been noted in roughly 25 per cent of the cases but they probably often have escaped observation. The lesion is very seldom larger than a pea, more often smaller. In hemorrhagic cases the nodules may reach the size of a robin's egg¹⁷ or larger and may become cystic and blood filled. The nodules which have been seen to appear in crops in various stages of the disease are hardly ever more than fifty in number. In order of frequency they have been observed on the forearm, chest, legs, abdomen.

¹⁰ Harris G. W. Periarteritis Nodosa Arch. Dis. Childhood 11: 31-44 1936

¹¹ Legros J. Periarteritis Nodosa or Kussmaul-Maier Disease. First Case Diagnosed in Infant During Life. Recovery From Therapy With Sulfapyridine and Acetylcholine. Arch. Françaises de Pédiat. Paris 2: 117-118 1944 1945

¹² Keeton L. W. and Bernstein J. C. Cutaneous Manifestations of Periarteritis Nodosa Arch. Dermat. & Syph. 40: 99-104 1939

¹³ Matras A. Zur Kenntnis Form und Pathogenese der Periarteritis nodosa. Wien. klin. Wchnschr. 51: 991 1938

¹⁴ Spiegel R. Periarteritis Nodosa Arch. Int. Med. 58: 993 1936

¹⁵ Rothstein L. J. Periarteritis Nodosa. Cutaneous Symptoms. Bull. New York M. Coll. Flower & Fifth Ave. Hosp. 3: 175-18 1940

¹⁷ Alkiewicz J. Multiple nekrotisierende Periarteritis nodosa der Haut mit Acanthosis nigricans Arch. f. Dermat. u. Syph. 188: 577 1933

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⁹⁶Abt A F. Erythema Annulare Rheumaticum. Am J M Sc 190 824 1935.

⁹⁷Carol W L L and Van Krieken J A. Histopathologie des Erythema annulare von Lehdorff und Leiner. Acta paediat 17 372 1935.

¹¹⁴Löwenstein Ernst. Die Tuberkelbazillämie in ihrer Auswirkung auf die Gesamtmedizin. Mit einem klinischen Teil von Carl Reitter. Wilhelm Neumann und Otto Kren. Leipzig und Wien 1935. Franz Deuticke.

¹¹⁵Urbach E and Blei R A. Erythema Annulare Rheumaticum (Lehdorff Leiner). Case Arch Dermat Syph 41 515-520 1940.

¹¹⁶Hench P G and Rosenberg E F. Palindromic Rheumatism. Proc Staff Meet Mayo Clin 18 809 815 1941.

¹¹⁷Kussmaul A and Majer H. Leber ein bisher nicht beschriebene eigentümliche Arterienkrankung (Periarteritis nodosa) die mit Morbus Bighill und rapid fort schreitender allgemeiner Muskellähmung einhergeht. Deutches Arch f Klin Med 1 484 1866.

¹¹⁸Harris A W Lynch C W and O'Hare J F. Periarteritis Nodosa. Arch Int Med 1163 1182 1930.

face back fingers scalp scrotum and tongue¹⁶ Sometimes a linear reticular or livedo racemosa like arrangement and pulsation indicate their connection with an artery^{13 128 19} This connection can be demonstrated better by capillaroscopy (Weigeldt after Boyd¹²⁶) The lesions are tender even painful and may be slightly raised purplish or red and surrounded by erythematous halos which may coalesce The center may appear grayish and depressed indicating necrotic changes¹² and a scab may appear on superficial nodules The nodular cases may suggest erythema nodosum¹⁵ The nodules have a tendency to heal leaving a tan colored pigmentation Mitras believes that the nodular type of periarteritis nodosa takes a more benign course

The second important cutaneous feature of the disease is *purpura* Petechiae and small purpuric spots sometimes with a white center¹⁵ are common sometimes abundant Large cutaneous extravasations (apoplexia cutanea)^{130 131 13} resembling purpura fulminans have been described by many authors¹²⁷ These hemorrhages may involve entire regions They may break down and form gangrenous ulcers of varying sizes depth and numbers^{131 131} sometimes climaxing in the mutilation of the acra of the extremities^{131 131} The coagulation time may be prolonged and the fibrinogen reduced to 50 per cent¹³¹

Besides the most characteristic features the nodules the gangrene roseola¹ and other erythemas and ephemeral rashes mentioned Pigmentation though not in the list compiled by Hare¹⁰ is a feature and may have the characteristics of Addison's disease¹³² Periarteritic involvement of the adrenals has in fact been reported in a few cases (Spiegel after Boyd¹²⁸) Edema and profuse sweating at night and moderate adenopathy are common symptoms

The *histological* picture is well established It shows infiltration of the walls of small and medium sized arteries with leukocytes and round cells of the Langhans type are common All layers especially the intima are thickened and the elastica and the muscle fibers are destroyed^{133 134} The proliferation of the intima leads to occlusion thrombosis and hemorrhage¹³⁵ Age Tissue and blood eosinophilia are frequently a conspicuous feature There have been reports of cutaneous fistulas it is often the site of a pythecrosis and of an inflammation usually characterized by infiltration with necroses in spots and numerous monocytes and giant cells Extravasations are exceedingly common

¹ Carol W L L and Praxen J R Periarteritis Nodosa Acta Dermatol Venereol 18 102 1937

¹² Goldschlag F and von Chwalibogowski A Letter Intern Fall von Periarteritis nodosa mit ausgedehnten Hauterscheinungen Arch f Dermat u Syph 171 677 1935

¹³ Feunil F Periarteritis Nodosa Arch Dermat & Syph 152 18 10 0

¹⁴ Löhe H and Rosenfeld H Multiple Hautgangrän bei Periarteritis nodosa Dermat Ztschr 61 99 3 0 1931

¹⁵ Hanowitch M M Tolayes S H and Charney R Periarteritis Nodosa Ann Int Med 11 119 1912

¹⁶ Potholm J L and Welt S Periarteritis Nodosa Am J Dis Child 11 1277 1933

¹⁷ Rich A R and Gregory J F Periarteritis Nodosa a Manifestation of Hyperactivity Bull Johns Hopkins Hosp 72 6 1943

¹⁸ Mochelet F Periarteritis Nodosa J Med Sci 101 337 339 1938

Scarlet Fever

Scarlet fever is caused by certain strains of hemolytic streptococci which are found mainly in the discharges of the upper respiratory tract. Contagion occurs predominantly among children from 1 to 5 years of age (rarely in infants) by close contact with patients and possibly though seldom through carriers or media such as milk toys or pets. The disease is most contagious during the first week. The incubation period is probably two days¹³⁶ but the observations vary from one to seven or more days. The onset is sudden with nausea and high temperature. A few convulsions and vomiting are common at this time but chills are uncommon. There are regularly early sore throat and a coated tongue. The scarlet fever exanthem appears after twelve to twenty four hours and reaches its height within five days the patient frequently being very ill. The fever gradually falls the rash fades and peels within three weeks and then recovery is reached unless complications develop. These complications include otitis media (14 per cent) arthritis (7 per cent) nephritis (4 per cent) and a number of rarer conditions (Hunt after Dick¹³⁶).

The mortality¹³⁷ in the United States is between 1 and 2 per cent in some communities much less this rate varies considerably during epidemics and in different countries. However approximately 4 000 deaths from scarlet fever occur every year in the United States. Except for the complications the post mortem findings are essentially negative. The diagnosis rests on the clinical picture especially the rash in connection with exposure to an epidemic and the occurrence of hemolytic streptococci.

Dermatomes — In rare cases the outbreak of the disease may be preceded by a transitory diffuse or spotted rash on the inner thighs¹³⁸. Such *fore exanthems* occur in other exanthematic infections too. Most of the new monographs on scarlet fever do not mention this rash.

The scarlet fever *exanthem* appears early often during the first day of the disease but occasionally the rash is delayed as much as five days¹³⁷. Diffuse erythema of the palate with red spots¹³⁶ marks the appearance of the exanthem. The exanthem is quickly followed by the skin eruption which starting at the neck creeps downward and reaches the feet in two to three days. The face usually remains free but it is flushed from fever. Morawetz¹³⁹ mentions that the exanthem involves the face. The area around the mouth stays pale with a yellow hue. This diffuse and relatively wide circumoral pallor includes the lips and often the chin. It is much wider and less sharply limited than the narrow perioral strip which often remains unaffected in various other inflammations and pigmentations about the mouth. The rash is often particularly pronounced on the femoral triangles on the abdomen and in the bends of the joints. Here the folds may appear more marked and slightly hemorrhagic (Pastia's lines).

¹³⁶Dick C. F. and Dick G. H. *Scarlet Fever* Chicago 1938 The Year Book Publishers Inc.

¹³⁷Toomey J. A. *Scarlet Fever* in J. B. Harrison's *Practice of Pediatrics* Hagerstown Md 1944 W. F. Prior Company Inc.

¹³⁸Schlossmann A. and Hottinger A. *Scarlet Fever* in Pfandl and Schlossmann *The Diseases of Children* Vol III Philadelphia 1933 J. B. Lippincott Company pp 76-169.

¹³⁹Morawetz C. *Acute Exanthema* *Scharlach* Handb. d. H. u. Gk. 24 419-4 1930.

The rash is a bright red erythema in which small punctate splashes can be discerned. On the extremities the pin point spots are less numerous and therefore better recognizable. These very small points are engorged papillae¹³⁵ and follicles^{139 140 142}. The swelling of the follicles and a slight infiltration of many of the red points may give a chagreen like impression to the hand. Mottling of the skin may be present on the extremities¹⁴⁴. In unusual instances the skin is edematous making the rash look like dermatitis. Minute clear rarely pustular¹⁴⁵ vesicles may be scattered over the red background. This phenomenon which is evidence of a more severe inflammation is known as *miliaria scarlatinosa*. The vesicles the content of



Fig 11 —Scarlet fever. Rash flushed face and circumoral pallor on third day. (Courtesy Dr. Max Fox)

which is alkaline do not correspond to the sweat glands. They may be abundant or even confluent forming large bullae¹³⁵. The erythema fades on transient pressure or when the skin is stroked with the fingernail and after ten to twenty seconds a white sometimes slightly icteric dermographism appears¹³⁹. Small numbers of *petechiae* are common especially in the flexures. The tourniquet test is usually positive and petechiae can easily be provoked by pinching. Edema of the dermis often causes slight puffiness of the face ears and fingers. The

¹³⁵ Unna P. G. Histopathologie d. Hautkrankheiten Berlin 1894. A. H. Schwald.

¹⁴⁰ Kritch N. Pachine A. and Sidow I. LA peau dans la scarlatine. Etude histologique. Arch. de Méd. et enf. 113 313 326 1919.

¹⁴¹ von Bormann F. Scarlet Fever. Review of Literature. Med. Klin. 37 661 664 1941.

¹⁴² Lehmann W. Streptokokkenkrankungen. Erg. ba d. inn. Med. u. Kinderh. 40 604 740 1931.

¹⁴³ Sobel N. in Mackee G. M. and Cipollaro A. C. Skin Diseases in Children. New York 1946. Paul H. Hoeber Inc.

¹⁴⁴ Liebmann C. Miliaria scarlatina a suppurativa. Med. Klin. 23 1368 1937.

exanthem reaches its full height during the second half of the first week. It then disappears often in the same order in which it came. During the period of involution the redness may still be pronounced in the evening although the skin appears pale in the morning. During the second week the skin becomes dry and the *desquamation* starts usually about the neck or on the lips sometimes at the sides of the face showing that in these cases the scarlet exanthem had involved the face also. The desquamation is at first branny, but in the third week the typical peeling in large flakes develops. The thick horny layers of the epidermis of the hands and feet are the last to go. The desquamation varies according to the intensity of the exanthem. While desquamation of fairly large shreds from the finger tips and toes is common the shedding of glove-like casts is quite rare. The epidermis which is ready to peel usually starts to crack under the toes and then peels off toward the tips as well as toward the soles. After a few days ragged flakes hang around the nails which in rare instances may come off also. It has often been said that the stripping of the shreds proximally from the nails over the digits is an almost diagnostic sign of preceding scarlet fever.



Fig. 11.—Scarlet fever. Desquamation.

Usually the exanthem does not itch. However the period of desquamation may be troubled by pruritus. Some cases of scarlet fever with a mild exanthem but unusually severe pruritus have been reported¹⁴⁶. In rare cases the rash may fail to develop or may be very light. The few cases are contagious and desquamation may or may not follow.

In true relapses of scarlet fever the exanthem may repeat itself^{148, 147} however true relapses are exceedingly rare. *Desquamation erythema*¹⁴⁸ or *erythema post*

¹⁴⁶Lortat Jacob L. Le prurit dans la scarlatine. La forme prurigineuse de la scarlatine. Presse méd. 12 07 '63 10 9.

¹⁴⁷Hübnerack F. Eberhard. Zu Klinik der Spätesantheme nach Scharlach. Monatschr. f. Kinderh. 89 1 17 1933.

¹⁴⁸Leiner Carl. Hautveränderung bei inneren Erkrankungen des Kindesalters. Wien med. Wchnschr. 79 1129 1929.

scarlatinosum is a dermatosis which is seen in less than 1 per cent¹⁴⁷ during the desquamation period or during relapses. In one type there are round or polygonal red slightly papular spots of fingernail size or smaller which have an accentuated deep red margin and a collar of scales. They cover the lower trunk, the buttocks and the thighs in a much less regular or pronounced pattern than the exanthem.¹⁴⁸ Another variety is a cracked net shaped erythema and dermatitis with desquamation.¹⁴⁷

Striae cutis distensae are not infrequently seen in adolescent girls after scarlet fever (see striae in chapters on puberty and pregnancy).

Moderate swelling of the superficial *lymphatic nodes* is common during the eruption. The nodes under the angles of the jaws which correspond to the tonsils are often infected. These and other neck nodes rarely other lymphatic glands may suppurate and break down.

The *oral* manifestations of scarlet fever are of great importance.¹⁴⁹ In the initial stage before the exanthem the pharynx is reddened and the tongue coated. The diffuse initial redness of the throat soon changes into the enanthem which consists of bright red or hemorrhagic points especially over the soft palate and the anterior pillars. The uvula and the hard palate are often left free and relatively pale. The tonsils become swollen early white exudate showing in the lacunae. The exudate may form diphtheroid membranes and necroses which may cover the entire tonsil. Ulceronecrotic lesions may even invade the tongue¹⁵⁰ and extend to the pillars and the soft palate.

The changing and characteristic appearance of the *tongue* has for more than a century been considered of great diagnostic importance but recently it has lost some of its import since typical scarlatinal glossitis occurs in only one half of the cases and may also be found in measles and German measles.¹⁵¹ The first changes in the tongue often precede the exanthem in scarlet fever.¹⁵¹ The early yellowish coating is soon pierced by the swollen red papillae fungiforms producing the strawberry tongue. The edges and the tip of the tongue usually become free early so that a red V shaped area results.

After about two days the yellow coating vanishes. On the fifth to eighth day the whole tongue is deep red and covered with raised papillae constituting the raspberry tongue.¹⁵²

Since the first description by Lister in 1858 (Klan¹⁵) a great number of cases of acute symmetric *gangrene* of the skin in scarlet fever have become known sometimes under names such as gangrenous purpura, purpura fulminans, or disseminated skin gangrene.

Suddenly sometimes after a mild or moderately severe course of scarlet fever usually in or shortly after the third week but occasionally as late as nine months after the onset¹⁵ patches of gangrene may appear on the skin often in a

¹⁴⁷Frask J O. Scarlet Fever Chap. XXI. New York 1910 Oxford University Press.

¹⁴⁸Berg r J. Ueber ein kretische Glossitis bei Scharlach. Monatchr f Kindch 38: 89 1908.

¹⁴⁹Cojan N. L'état de la langue dans la scarlatine au moment de l'éruption. J de méd de Paris 1902 1911 1912.

¹⁵⁰Klan H. Akute asymmetrische Hautgangrän bei Scharlach. Klin Wochenschr 18: 1538 1937.

¹⁵¹Dick C F. Williams F M and Edmonson H. Gangrene in scarlet fever. Am J Dis Child 1937 374.

¹⁵²374 1937.



Fig 15

Fig 16

Fig 15—Scarlet fever tongue on third day. Coating is pierced by swollen papillae fungiformes. Strawberry tongue. (Courtesy Dr. Max Fox.)

Fig 16—Scarlet fever fourth to fifth day. Tongue is swollen and desquamated along the edges. (Courtesy Dr. Max Fox.)



Fig 17

Fig 18

Fig 17—Scarlet fever fifth day. Tongue is swollen and the dorsum is also getting edge till coated on the anterior soft palate. (Courtesy Dr. Max Fox.)

Fig 18—Scarlet fever between fifth and eighth day. Tongue is red studded with swollen papillae. Rhabdomyolysis. (Courtesy Dr. Max Fox.)

symmetrical distribution. They occur most frequently on the legs, the buttocks and the genitalia¹⁸⁴ occasionally on the arms, hands, face and chest¹⁸⁵. They range in size from small patches to that of a whole region, such as an entire foot or hand. The involved skin undergoes the well known sequence of changes of gangrene: pain, erythema, dark discoloration, blistering and finally demarca-



Fig. 19



Fig. 20

Fig. 19—Patch of gangrene after scarlet fever. Petty's gangrenousum. (Courtesy Dr. Max Fox)
Fig. 20—Foot gangrene after scurvy. (Courtesy Dr. Max Fox)

tion and slough. The hemorrhagic discoloration is not evidence of a hemorrhagic diathesis. The healing tendency is often surprising. The outcome depends upon the size of the lesions, the necessity for amputation and the presence of other complications. The mortality is probably lower than 50 per cent.¹⁸

¹⁸⁴Huber H. J.
Praxis 8: 5-11, 1937.
¹⁸⁵Witz B. F.
27: 1019, 1933.

Fin B. Itag zur G. nitalgangren b. i. Frisalp. i. m. f. d. h. n. i. ind. salter. I. ind. ärztl.
Multiple Gangren of the Skin Following Scarlet Fever. Arch. Dermat. & Syph.

The cause of this multiple symmetric gangrene is still little understood. Purpura capillary thrombosis and thrombophlebitis¹⁵⁶ have in several instances been shown not to be causative. Purpura has occasionally been present^{157 158}. The findings in amputated limbs failed to demonstrate arterial block^{15 153} and the findings of phlebitis were more suggestive of a sequel than of a cause. Possibly the explanation may be found in allergic phenomena. Gangrene has often been observed during the third or fourth week, the typical time of post scarlatinal nephritis and has actually been seen together with it.

Another rare complication of scarlet fever is *thrombophlebitis migrans*. This is an acute febrile phlebitis usually involving the veins of both legs^{156 160}.

Circumscribed edema is another rare sequel of scarlet fever¹⁶¹. It has been known for a long time but it is apparently seen only in some epidemics. Steinbrinck¹⁶ reported forty cases of edema of the upper lids in a recent epidemic. The swelling was in some instances so severe that it suggested subluxation of the eyeball. Involvement of the paranasal sinuses probably plays a part. All the skin changes discussed under the heading of septicemia may be observed occasionally.

Purpura though relatively rare in scarlet fever may occur just as in the course of other infections. It has been seen most often during the third week. The platelet count may be normal¹⁶² or low. The mortality is high¹⁶⁴. Hemorrhagic tendencies can be demonstrated early.

The *tourniquet test* is commonly positive in scarlet fever in fact it had been devised first as a diagnostic procedure in scarlet fever¹⁶⁵. Lately the capillary resistance has been investigated by C. E. Brown¹⁶⁶ with the more exact Dalldorf¹⁶⁷ suction method. It can be shown that the capillary resistance as expressed by the number of petechiae provoked under certain conditions is low at the onset and increases as the patient recovers. Age of the patient¹⁶⁸ toxemia and marked desquamation may lower the resistance¹⁶⁶. Myrgård¹⁶³ saw wavelike recurrences of lowered resistance in intervals of about two weeks. He¹⁶⁶ demonstrated that

¹⁵⁶Hueneken F. J. and Silverstein D. M. Post scarlatinal Phlebitis. Am. J. Dis. Child. 26: 447-1933.

¹⁵⁷Box Ch. R. and Masingham R. Purpura Haemorrhagica Complicating Scarlet Fever. Lancet 1: 295-96 1931.

¹⁵⁸Mundt Odd. Purpura mit angedeuteter Hautnekrose bei Scharlatina. Norb. Mag. f. Lægevidensk. 92: 14-16 1931.

¹⁵⁹Rusch Erich and Gottlieb Philip M. Allergy. New York 1943. Grune & Stratton Inc.

¹⁶⁰Bates J. V. Post scarlatinal Thrombophlebitis Migrans. Brit. M. J. 1: 665 1943.

¹⁶¹Zehlin H. Ein ungewöhnliche Form von Scharlach. Abhandlung b. d. Scharlach. München med. Wchnschr. 81: 1960-1936.

¹⁶²Steinbrinck W. Unusual Complication (Scarlet Fever). Deutsche med. Wchnschr. 68: 1149-1942.

¹⁶³Myrgård A. and Enström N. Consideration of Phnomnon of Purpura Following Scarlet Fever. Am. J. M. Sc. 196: 3-1 1932.

¹⁶⁴Wood Smith F. B. Purpura as a Complication of Scarlet Fever. Brit. J. Child. Dis. 28: 273-51 1931.

¹⁶⁵Leede G. Tourniquet Test in Scarlet Fever. Münch. med. Wchnschr. 68: 293 1911.

¹⁶⁶Brown F. F. Scarlet Fever—Capillary Resistance. Arch. Pediat. 47: 553-55 1940.

¹⁶⁷Dalldorf H. A Criticism of Hemorrhagic Diathesis in Experimental Scurvy. J. Exper. Med. 53: 289-1931.

¹⁶⁸Myrgård A. Capillary Resistance and Vascular Test in Scarlet Fever. Upsala Läkart. förh. 37: 417-430 1932. Zbl. 44: 197.

Fig 21



Fig

- Fig 21 —Severe purpura after scarlet fever (Courtesy Dr Max L. J.)
 Fig 22 —Non-severe purpura after scarlet fever (Courtesy Dr Max L. J.)

the absorption time of a saline wheal (McClure Aldrich test¹⁰⁹) is shortened especially in the beginning and in toxic cases.

Capillaroscopy shows even in the early period the capillaries to be lengthened and engorged on the arterial side. The subpapillary plexus is hyperemic and plainly visible on a brownish background. The arterial flushing yields later to a status with both sections of the capillaries about equally filled with cyanotic blood. It is more than five weeks until the capillaries appear bright red again on a rosy background with sharply outlined margin and a hardly discernible subpapillary plexus.¹¹⁰



Fig. 3.—Purpura after scarlet fever. (Courtesy Dr. Max Fo.)

The *Dick test* for susceptibility to scarlet fever is based on the neutralization of scarlet fever toxin in the skin of the person tested. Exactly 0.1 c.c. of the test solution is injected intracutaneously.¹¹¹ The test is considered positive if after twenty to twenty-four hours an erythema however slight of not less than 10 mm. in any diameter is present. The reading should be done in bright light. Induration is not required and may even be absent in strongly positive reactions. A positive reaction shows that the person is susceptible to scarlet fever. The test is usually negative in the newborn infants of immune mothers but becomes positive during the first year of life.

¹⁰⁹McClure W. and Aldrich C. A. Time Required for Disappearance of Intradermally Injected Salt Solution. J. A. M. A. 81: 993-94, 1923.

¹¹⁰Müller-Ottfried. Zur Beobachtung des Capillaritätslaufes beim Scharlach. Verhandl. d. deut. ch. Kongr. innere Med. 11: 20, 1911.

The newborn infant of a nonimmune mother usually reacts positively. In later life the reaction depends on the degree of exposure and silent immunization. In a group of children who grow up in crowded conditions for example in an

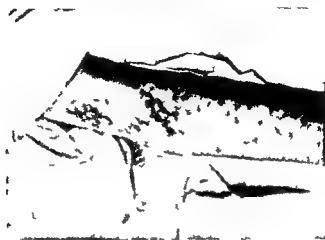


Fig. 24—Positive Rumpel sign (L. side-Rumpel sign) in scarlet fever (Courtesy Dr. Max Fox)



Fig. 25—Negative blanching test in scarlet fever (Courtesy Dr. Max Fox)

institution the incidence of susceptibility may be as low as 10 per cent and in rural groups with few contacts it may be as high as 85 per cent.¹⁷⁰ The morbidity among children in Milwaukee with negative reactions to the Dick test was found to be only about one fourteenth of the general morbidity (Cummings after von Bormann¹⁷¹). Convalescents of scarlet fever have negative Dick tests

¹⁷⁰von Bormann F. "Scharlach Monat chr f Kind rh 83 213 261 1910

In rare instances a mild miniature scarlet fever may follow the Dick test ¹⁷

The *blanching or Schultz Charlton test*¹⁷³ (Ausloschphänomen) is based on the local blanching of the scarlet fever exanthem by an intracutaneous injection of normal serum serum of convalescent scarlet fever patients or serum of diluted antitoxin in amounts of 0.1 to 0.5 c.c. A positive reaction consists of blanching of the rash eighteen to twenty four hours after the injection in a zone surrounding the central red spot where the injection was made ¹⁷⁸ The positive Schultz Charlton test¹⁷³ supports the diagnosis of scarlet fever The area of skin which has been blanched does not peel ¹⁷⁴

There is still controversy about the limitations of these two tests ^{175 176}

Pathology—There is edema hyperemia and inflammatory infiltration especially around the follicles and sweat glands Endothelium covered fibrous exudates have been seen in the walls of small veins in scarlet fever as well as in other pyogenic infections ¹⁷⁷ especially subacute bacterial endocarditis Parakeratosis precedes the peeling ¹⁴¹

It is remarkable that hemolytic streptococci are common in the superficial scales of the peeling skin but could rarely be found in the deeper layers ¹⁷⁴ This may mean that the scales become infected from without and that the living skin during the desquamation is no longer infected Recently streptococci have been demonstrated in the endothelial cells of blood and lymphatic capillaries and in adjacent cells ¹⁷⁹ The desquamated skin is not considered contagious ¹⁴⁴

¹⁷¹Wallis H R E. Manifestation of Scarlet Fever After Dick Test Lancet 2 19 194

¹⁷²Schultz W and Charlton W. Serologische Beobachtungen am Scharlachexanthem Ztschr f Kinderh 17 328 333 1918

¹⁷³Fanconi C. Beiträge zum Scharlachproblem. Abhandlungen aus der Kinderheilkunde und ihren Grenzgebieten N 13 Berlin 1926 v Ka ger

¹⁷⁴Reisman H A and Berkow A. Dick Test Arch Pediat 58 246 93 1941

¹⁷⁵Press E and Litvak A M. Schultz Charlton and Dick Tests in Scarlet Fever Arch Pediat 58 194-197 1941

¹⁷⁶Siegmund H. Gefäßwandreaktion an Verhältnissen der pathologischen Gesellschaft 20 261 19 5

¹⁷⁷Kanevskaya M J. Presence of Streptococci in Scales of Scarlet Fever Patients JAMA 89 1011 19 7

¹⁷⁸Tornack J H. Etiology and Pathogenesis of Scarlet Fever Histologically Demonstrated Storage of Coccus-like Structures in Endothelial Cells of Skin Mucous Membrane and Lymph Nodes Klin Wchnschr 21 581 194

CHAPTER III

SYSTEMIC INFECTIONS

Lobar Pneumonia

In none of the various types of lobar pneumonia are skin manifestations important with the exception of *herpes simplex* (herpes febrilis herpes symptomaticus) which occurs in a high percentage between the second and fifth day usually on the lips. The eruption appears as groups of clear vesicles on a red slightly edematous base. After one to two days the vesicles become pustular often confluent and finally they dry up. The crusts come off after about five days usually without leaving a scar. The incidence of herpes varies according to the type of pneumococcus. Among 500 cases of lobar pneumonia of all types 30 per cent were herpetic.¹⁸⁰ This incidence was observed in London, England. The herpes incidence among 500 cases in New York was only 12 per cent¹⁸¹ while many older, mostly German, figures run as high as 40 or even 50 per cent. J. A. Montgomery¹⁸² analyzed the occurrence of herpes in 500 cases of lobar pneumonia with regard to types of pneumococci. While the incidence of herpes is about the same (30 per cent) in all types, the mortality in the herpetic is lower than in the nonherpetic cases, especially in type I in which the mortality is less than one sixth of that of the nonherpetic of the same group. The relatively favorable prognosis of herpetic pneumonia has been well established^{183 184 185} for a long time. Montgomery¹⁸⁶ records a mortality of 14 per cent in the herpetic group and 16 per cent in the total. Schwartz's¹⁸⁷ corresponding figures are 5 and 25 per cent which is closer to the old figures.¹⁸

Herpes is uncommon in acute Friedländer pneumonia which has a high mortality (75 per cent).¹⁸⁸

Petechiae occur in every case of pneumococcic sepsis. E. Fraenkel¹⁸⁹ examined such lesions in two fatal cases. Clinically they seemed to be only petechiae; the histological structure suggested bacillary metastases but no pneumococci could be found. E. Fraenkel¹⁹⁰ emphasizes the rarity of skin manifestations in pneumococcic infections. He believes that the skin enjoys a certain immunity to pneumococci since skin metastases are lacking even when specific metastases are found in many other organs.

¹⁸⁰Montgomery J. A. Herp. Febrilis in Lobar Pneumonia. *Lancet* 1: 1041-1042, 1939.

¹⁸¹Schwartz J. Pneumonia, 500 Cases. *M. Rec.* 147: 19, 200, 1938.

¹⁸²Schönfeld W. Die klinische Bedeutung des Herpes simplex und der Krankheiten und pathologischen Zustände. *Tung Ch. med. Monatchr.* 12: 296-302, 1937.

¹⁸³Nagel O. Herpes simplex. *München. med. Wchnschr.* 83: 339-344, 1936.

¹⁸⁴Coddall M. Life Story of Simple Herpes. *Lancet* 1: 906, 1939.

¹⁸⁵Solomon M. Chronic Friedländer Infection of the Lung. *J. A. M. A.* 118: 257, 1936, 1940.

¹⁸⁶Fraenkel E. Metastatische Dermatoen bei akuter Bakteriell. Allgemeinerkrankung. *Ztschr. f. Hyg. u. Infektionskrankh.* 76: 167, 1914.

Equally rare are diffuse or maculovesicular *erythemas*^{187 188} A few times pneumococci have been found in the skin lesions The rare varicella resembling rashes may be generalized herpes¹⁸⁹

As long as the fever is high the skin remains hot and dry It is an old observation that the *cheek on the side of the involved lung is redder* than the other The most plausible explanation is that the patient often lies on the involved side in order to keep this painful side quiet but this explanation is not always correct¹⁸⁷ Only during and after the crisis do profuse sweats occur especially in juveniles These sweats are sometimes followed by *miliaria rubra*

Systemic *Pyocyaneus* Infection

In spite of the common infection of wounds with *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*) and of the frequent saprophytism of this microorganism systemic infection is rare and occurs usually in debilitated persons^{190 191 19} Almost all organs may become infected the skin often being involved The skin manifestations of severe pyocyaneus sepsis do not differ from those of other pyemids However there is a characteristic dermatosis *ecthyma gangraenosum* which is known to occur in the wake of measles and various other infections and cachectic states (see Fig 19) especially in children and which in a considerable number of instances has been shown to be caused by *Pseudomonas aeruginosa* Its character as a skin manifestation of a generalized infection is shown by many analogous autopsy findings in internal organs¹⁹⁰ The skin lesions start as papules but soon become bullous and hemorrhagic and form round sharply outlined necrotic and painful ulcers which may reach the subcutaneous tissues and even invade the muscles Petechiae and large ecchymoses are supposed to be characteristic⁶⁵ Their number varies from one lesion to exanthematic dissemination Healing has seldom been observed since most of these patients die within a short time The general course is that of a septic toxemia¹⁹⁰

The histologic examination shows many gram negative bacilli in the outer layer of the blood vessels especially of the arteries¹⁹² Atypical apparently hematogenous skin infections with pyocyaneus have occasionally been described^{190 193}

Meningococcic Meningitis (Cerebrospinal Fever)

After an incubation period of a few days the onset is usually sudden with high fever severe headache and vomiting Meningitic symptoms ap

¹⁸⁷Howard C P and Mills E S *Pneumonia* Oxford Monographs Vol V New York 1939
Oxford University Press

¹⁸⁸Schmitt LaBaume F and Otto C *Zur Histologie und Pathogenese der Pyokokkenkrankheiten* Arch f Dermat u Syph 169 431-435 1933

¹⁸⁹Sharp Wm G *Eruption resembling Varicella in Lobar Pneumonia* Brit M J 1 11 1929

¹⁹⁰Bruck C *Die Pyocyaneuskrankungen der Haut* Handb d H u Chk 9 1 125-144 1908

¹⁹¹Klein B G and Vachek A S *The Fatal Cases of Bacillus Pyocyaneus Infection* JAMA 98 525-532 1932

¹⁹²Lewandowsky F *Über die Hautaffektionen bei Erwachsenen verursacht durch den Bacillus pyocyaneus* Münch m med Wchnchr 1907 II 5

¹⁹³Frel W and Wiener K *Ein Fall von ulceröser Hautkrankung aus der Gruppe des Ecthyma gangraenosum (mit Pyocyaneusbefund)* Arch f Dermat u Syph 134 106-118 1911

pear after from two to four days. There is irregularity of the pulse and respiration, painful stiffness of the muscles, abolition of superficial abdominal reflexes, insomnia and restlessness. The patient lies on his side with the knees drawn up. The leukocytosis may be very high.

After the first week the patient's restlessness often changes to stupor. The recovery is gradual, the course is varying, death may occur in any stage.

Before the advent of the sulfonamides the mortality rate was as high as 49 per cent in children under the age of one year and from 10 to 20 per cent above this age.¹⁹⁴ Today the mortality rate has been lowered to 2 per cent¹⁹⁵ and even less.¹⁹⁶

The sulfonamides and penicillin are the drugs of choice in the treatment of meningococcal infections.

Dermadromes—A variety of rashes occur with varying incidence. Figures between 91¹⁹⁷ and 100 per cent¹⁹⁸ are available.¹⁹⁸



Fig. 96—Meningococcal meningitis. Purpuric rash. (Courtesy Dr. Max Fox.)

Of importance is a *purpuric rash* consisting sometimes of only a few petechiae, occasionally of very many hemorrhagic spots resembling flea bites or larger. The rash often being scanty, one should look for purpuric lesions on the chest, armpits, abdomen, thighs, buttocks, and hips. A single petechia of the conjunctiva may

¹⁹⁴Worster Drought, C. and Kennedy, A. M. *Cerebro-spinal Fever*. London, 1919. A. & C. Black Ltd.

¹⁹⁵Thomas, H. M. Jr. Meningococcal Meningitis and Septicemia. *J. A. M. A.* 123: 261-270, 1943.

¹⁹⁶Miller, I. W. and Miller, H. S. Meningococcal Infection in an Army Camp. *J. A. M. A.* 123: 9-14, 1943.

¹⁹⁷Blackerby, P. F. and Caudill, E. W. Epidemiologic Study of Approximately 400 Cases of Cerebrospinal Meningitis: Comparative Value of Antitoxin and Antibacterial Serum. *South. M. J.* 21: 161-168, 1934.

¹⁹⁸Dickson, R. C., McInnon, N. E., Wagner, D. and McMillan, N. B. Meningococcal Infection. *Lancet* 1941 II: 631-634.

be the only lesion.¹⁹⁶ The purpuric rash may develop exceedingly rapidly almost under the eyes of the observer. There is no parallel between the extent of the rash and the severity of the infection¹⁹⁶ as had been thought by many older authors.¹⁹⁴ However, purpura seems to be of more ominous significance than petechiae¹⁹⁶ and the fulminating purpura of the Waterhouse-Friderichsen syndrome is an almost certain omen of a fatal outcome. Larger purpuric lesions may become vesicular, bullous or ulcerative. Petechiae are not restricted to the skin. They may appear in the conjunctivae, in the oral mucosa and in the serous membranes. The great significance of the purpuric rash lies in the fact that the



Fig. 97.—Meningococcal meningitis. Papulohemorrhagic rash (Courtesy Dr. Max Jo).

lesions are true *metastatic bacillary lesions*, not hemorrhages due to lowered capillary resistance of toxic cause. E. Fraenkel⁶⁷ found meningococci in the cellular infiltrate of the petechial efflorescences. He also demonstrated Friedländer bacilli in the purpuric skin lesions of a case of meningitis caused by this microorganism. Since then the search for microorganisms in purpuric lesions has become a diagnostic method. Tompkins¹⁹⁰ and McLean and Caffey⁹¹ were able to demonstrate diplococci in smears in 80 per cent of their cases. To obtain material for the smear, a purpuric spot is gently blanched between two fingers and pricked with a fine hypodermic needle. Then some serum is squeezed out and

¹⁹⁶W. W. W. and Frank E. M. Summary of 50 Cases of Cerebrospinal Fever. *U. S. Navy M. Bull.* 41: 960-977, 1913.

¹⁹⁰Tompkins V. N. Diagnostic Value of Smears From Purpuric Lesions of Skin in Meningococcal Disease. *J. A. M. A.* 123: 31-3, 1943.

⁹¹McLean S. and Caffey J. Endemic Purpuric Meningococcus Bacteremia in Early Life. The Diagnostic Value of Smears From Purpuric Lesions. *Am. J. Dis. Child.* 42: 103-107, 1931.

Fig 28

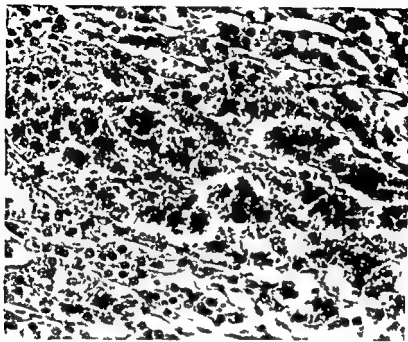


Fig 29

Fig 28—Fulminating meningococcemia (Waterhouse-Friderichsen syndrome). Engorgement of capillaries in zona fasciata with early hemorrhagic extravasation (from Iratt Thomas Kelly and Gaze, South Afr J 1945)

Fig 29—Fulminating meningococcemia (Waterhouse-Friderichsen syndrome). Meningococci and polymorphonuclear leukocytes in smear from purpuric lesion (Giemsa stain, X 600) (from Iratt Thomas Kelly and Gaze, South Afr J 1945)

placed on a slide. Quantity is not an object but it is important that the prick be superficial and the exudate not diluted by peripheral blood. The smear is stained with Giemsa or Wright stain. The smears taken from lesions other than purpuric ones are usually negative.

The second type of cutaneous manifestation in meningococcic infection is a *maculopapular rash* which is sometimes seen as early as on the first day of illness. It is described as consisting of discrete slightly palpable rather



Fig. 30.—Herpes labialis in meningococcic meningitis. (Courtesy Dr. Max G.)

cantly (rarely more than a dozen) inconspicuous round well defined pink spots of from 5 to 35 mm in diameter^{195 0}. The eruption may coincide with or closely follow the onset or a recurrence of the fever and the general symptoms of the infection^{191 00}. The lesions are most often found on the trunk and along the extremities especially about the shoulders. They are tender, do not appear in crops and vanish within about four days. Sometimes they become purpuric in the center and palpable like erythema nodosum. Only rarely have they a morbilliform character but they often resemble the rose spots of typhoid fever to such a degree that all other diagnostic factors must be considered in order to avoid errors. An early appearance especially on the extremities seems to indicate meningitis rather than typhoid. During epidemics this rash alone is considered characteristic enough to establish the diagnosis of meningococcic septicemia.

¹⁹¹Herrick, W. W. Meningococcal Infection. Oxford Medicine Vol. I New York 1940. Oxford University Press pp. 71-106.

¹⁹⁵Pylest, H. 204 Cases of Cerebral Fever. J. Roy. Army Med. Corps 76: 249-60, 1941.

Several other types of cutaneous lesions have been described. They include transient rubelliform⁶⁴ or scarlatiniform erythematous rashes, hemorrhagic vesicles, hemorrhagic gangrene²⁶⁵ and a peculiar urticaria consisting of a large wheal on the buttocks. The latter, which has been seen by several authors, was supposed to be a foreshadowing of a fatal outcome¹⁸⁴ in the pre-sulfa era. *Herpes* often extensive and in atypical distribution is present in about one third of the cases. While often seen on the fourth day, it may appear at any time after thirty-six hours from the onset.⁹³ *Herpes zoster* involving almost all of the known sites is conspicuously frequent, as in lobar pneumonia. The vesicles may contain meningococci. The belief that herpes is a favorable sign was held by many of the earlier authors; however, this is not true. The opinion was probably caused by the relatively favorable prognosis of herpetic pneumonia.

Gonorrhea

Gonorrhea is predominantly a disease of the mucous membranes. Cutaneous involvements are rare. Ulcerations of the genital skin, folliculitis and abscesses or pseudoabscesses are mostly due to exogenous infection of epithelial ducts or follicles from the gonorrheic urethra. Hematogenous gonococcal infections of the skin can be grouped under *transitory* urticarial, erythematous or hemorrhagic exanthems of the type seen in other bacteremias and *keratotic* eruptions which are characteristic of gonorrhea and hardly known in other diseases.

There is a great morphologic variety of exanthems in the former group, which makes it difficult to correlate the rash with the gonorrhea by any other evidence than coexistence, even after the possibility of an eruption from sandalwood oil, cubebs and similar drugs used in gonorrhea has been ruled out. The eruptions which have been described have been seen not only in febrile septic cases but also in relatively mild infections. If they repeatedly come and go with exacerbations of the gonorrheic infection, the connection is quite obvious. The best proof of the specific nature of the questioned eruption is, of course, the finding of gonococci in the skin lesion. This has been accomplished in several cases.²⁶⁸ In one case of septicemia caused by gonococci, a macular rash was seen together with arthritis and endocarditis.²⁶⁷ Gonococci could be demonstrated in the blood in the endocardium and in the erythematous spots. Kerl⁹⁸ saw simple erythema together with epididymitis. Scarlatiniform²⁶⁹ urticarial eruptions with hemorrhagic tendencies occupying the lower legs,²¹⁰ vesicular²⁶⁶ vesiculohemorrhagic²¹¹

²⁶⁴Silverthorne N. and Cameron C. Meningococcus Infection. *J. Pediat.* 19: 618-67, 1941.

²⁶⁵Polisso H., Claudio P., Auban J. J. and de Balmain A. Meningococcemic Gangrenous Purpura Associated With Cerebrospinal Meningitis. Cur. by S. rotherapy Sulfanilamide and Vitamin A. *Bull. et mém. Soc. méd. d. hôp. de Paris* 55: 891-896, 1939.

²⁶⁶Margolin E. B. Gonorrheal Dermatitis as Part of Systemic Gonorrhea. *Urol. & Cutan. Rev.* 47: 512-514, 1943.

²⁶⁷Dörner L. Gonokokken eptis. *München med. Wchnschr.* 70: 1069, 1923.

²⁶⁸Kerl W. Gonokokk exanthem. *Zbl.* 49: 537, 1935.

²⁶⁹Cojan G. Septicémie gonococcique récidivante avec détermination rare. *Rev. roum. d. Urol.* 3: 498-507, 1946. *Zbl.* 56: 346.

²¹⁰Sullivan S. J. Cutaneous Eruption Accompanying Gonorrhea. Case of Hemorrhagic Exanthem. *Urol. & Cutan. Rev.* 28: 93-95, 1934.

²¹¹Kell H. Type of Gonococcal Bacteremia With Characteristic Hemorrhagic Vesiculo-Pustular and Bullous Skin Lesion. *Quart. J. Med.* 7: 1-15, 1938.

hemorrhagic ^{14 212 213} nodular ²¹⁴ herpetiform ²¹⁵ erythema exudativum multiforme and erythema nodosum resembling rashes ^{10 16 17} are an illustration of the multiplicity of appearances which these bacteremic eruptions may assume ²¹⁵ Sometimes these rashes show very distinctly that they are caused by focal infections Sullivan ¹⁰ observed an acute eruption of suppurating nodules after dilatation of a urethral stricture

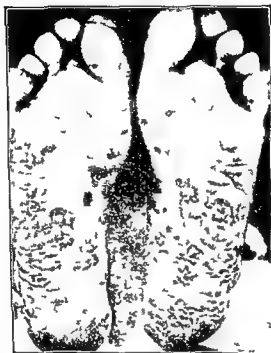


Fig 31 —keratosi gonorrhoea (Fom Epitel E Am J Syph 21 143 1937)

In some instances gonococci have been found in purpuric lesions (Bruu gard and Tjotta after Langer ¹⁵) and in abscesses. Icterus is mentioned in several cases ¹⁸. In spite of the great morphologic variety these bacteremic gonococci are rare and do not differ much from the eruptions seen in pyogenic septicaemia.

Wiedmann A. Beitr. z. Patholog. der Gef. skrankung n. d. Haut d. gew. f. lichen
Veränderungen beim hämorrhagischen Gonokokk xanthom mit hämorrh. B. u. histolog. Gef.
Gefäßveränderung. D. Dermat. Wochenschr. 98: 541-54. 1933

of Case In Which Penicillin was Used A Ch D smat & Gypb 54 150 178 1946

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1941 1 Aetiologie d s Eryth ma nolo tum 271 38 712 1931

Dermit & Ir 34 511 517 1933 Zbl 48 2 1

111 Murdock, J. G. A Case of Everted and Blenorrhagicum Brit. J. Ven. Dis. 12 242-244 1936

Of much greater dermatological interest are the rare *hyperkeratoses* in gonorrhea *keratoderma blennorrhagicum* (*keratosis blennorrhagica*). Only 166 cases have been described since Vidal's¹ first observations in 1893. It has been estimated that *keratosis blennorrhagica* occurs about once in 5 500 cases of gonorrhea.²¹ These dermatoses form a clinical picture which is almost exclusively connected with gonorrhea and it certainly is one of the most characteristic dermatomes peculiar to any one infection. Most of the patients are young men suffering from chronic urethral gonorrhea usually with complications particularly arthritis and ocular complications. The gonorrheal infection frequently is of long standing—often many years when the rash breaks out. The eruption often starts with a papulovesicular exanthem. In some cases the primary lesion is described as a small glossy pink papule resembling a droplet of wax. The vesicles dry up but instead of peeling as one would expect they transform into pseudopustular lesions which look yellow but do not contain pus. These become keratoses and finally form a large hobnail shaped conical lesion of layer texture. The keratoses are rupoid impet shaped and have a flat or umblicated top with a yellow center which contains brittle white horny detritus. The bottom layer of horny material forms a yellow clifflike ring around the lesion which is sometimes surrounded by an inflammatory areola. The keratotic top is easy to remove leaving a shallow pink slightly moist or gelatinous erosion. Keratoses at these areas are often of follicular origin. The lesions may grow slowly from pinhead size to several centimeters in diameter and they may coalesce into large rough hyperkeratotic plaques mostly on the soles and around the big joints particularly if the joints are inflamed. In these plaques many pseudopustular cavities may be found. The extremities are in some cases studded with button or medallion shaped lesions which may reach 1 cm in thickness. The *penis* is a site of predilection for the gonorrheic dermatomes² which may appear as typical keratotic papules. On the glans and on the inner surface of the foreskin they may appear as glossy red flat papules or macules³ which may coalesce into polycyclic patches. Sometimes the keratotic character of these lesions is marked by a grayish ulcerated crumbling horny top layer (*balanitis circinata*). The *keratoderma* may even be restricted to such penile eruptions. These lesions occasionally resemble a syphilitic chancre (Tullien after Langer¹⁵) or lichen planus.

The *scalp* sometimes becomes involved.²⁴ The *nails*⁴ often become thick dull and brittle and subungual keratoses may raise or loosen the nail. The

¹Vidal E. Éruption généralisée de pustules cornées avec chute d'ongles. *Ann. f. dermat. et syph.* 4 3 1893.

²Cotroming L. Quêlque considération sur la kërato blennorrhagique. *J. d'uroi.* 32 251 1937 1931.

³Scholtz M. Gonorrheal keratoderma. *Arch. internat. & Syph.* 11 961 969 1930.

⁴Arning and Meyer D. H. On Hyperkeratos. *Balanitis circinata gonorrhoeica*. *Abh. f. r. Vorhau.* *Arch. f. Dermat. u. Syph.* 108 3 26 1911.

⁵Sherman W. L. Blumthal F. and Heldreich J. Blennorrhagie Balaniforme keratoderma. *Arch. internat. & Syph.* 39 422 429 1939.

⁶Frühwald I. Keratosis blennorrhagica. *Zbl. B.* 11 1953 1935.

⁷Cederberg A. Abortivformen der gonorrhoeischen keratoderma. *Acta dermat. ven. col.* 13 43 2 193.

⁸Cornbl et T. and Pac F. R. Keratoderma Blennorrhagicum. *Arch. Dermat. & Syph.* 20 91 1934.

whole nail bed even the entire tips of the fingers or toes may be covered with the keratotic masses. In several instances sharply contoured round or poly cyclic irregular grayish patches with erythematous borders have been observed on the palate and on the buccal mucosa^{23 27 3 9}

The general distribution of the rash is largely symmetrical. All degrees of involvement from a single keratotic patch on the penis⁴ to universal erythroderma have been seen. Naturally the discomfort and suffering of the patient depends on the extent and the degree of tenderness of the individual lesions. The appearance of new crops is usually coupled with renewed arthritic attacks. The eruption may last months or years depending mainly on the course of the gonorrhea but also on the degree of involvement of the skin. The majority of the cases of keratosis blennorrhagica finally heal but about 10 per cent fatalities have been recorded^{23 1}

The histological picture is characterized by heavy keratosis and parakeratosis with formation of cavities. There are edema and cellular infiltration in the papillary stratum.

Gonococci have been found in typical lesions in at least seventeen instances^{13 9 30} although much more often the efforts to find the microorganisms have been in vain. The positive findings are definite proof of the hematogenous infectious nature of the eruptions which already had been suggested by the clinical relationship to arthritis endogenous conjunctivitis and iritis and the symmetric and follicular distribution on the extremities. Occasional observations give further support to the conception of a focal infection. Scholtz¹ saw a flare up of the joint symptoms and the appearance of a new crop of heavily crusted lesions after 8 c.c. of gonorrheal vaccine (instead of 0.8 c.c.) had been administered by mistake. Similar reactions have been seen after treatment with vaccine³¹ and warnings against vaccine therapy of such hyperergic patients have been voiced³⁷. The extirpation of the infected seminal vesicles resulted in the healing of a gonorrheic exanthem and the dilatation of a urethral infiltration or other urethral manipulations produced flare ups³ in at least five instances¹³ (Lewin after Langer¹⁰). These observations are not only evidence that the gonorrheic keratoderms are caused by focal infection but they show the role allergy plays in producing the characteristic clinical entity. The scarcity of the gonococcus has its analogy in the paucity of microbes in tuberculids trichophytids and other

² Fri W. Con E. nth m d r Mundsclieinhaut Balanitis et c. nata in no. h. sca b. i. Circumcidit m. Zbl 44 371 1933

³ Col and Dri. K. ratolerna Bl. norrhagica Arch. H. rnat. & Syph 19 836-837 19 9

³³ Barrett C. C. K. ratolerna Bl. norrhagica two case. Gono. o. cu. in. Lo. al. Le. on. A. h. Dermat. & Syph 22 6 7 736 1930

³¹ Comb s. b. C. a. d. B. h. man. H. T. U. of Vitamin A in I. al. I. Bl. norrhagica Arch. Dermat. & Syph 46 7-8 33 1940

³² Scmazioni T. Ch. ated. rnia. bl. n. rragica. Cio. ital. di. d. rnat. H. 2 36-38 1931 Zbl 33 30

³³ Faib. rbe. H. Tréthritus à gon. e. qu. récidiv. ntes. arthropathie multiples t. ubl. trophiques. J. d. mal. cutan. et syph 1900 Ca. méi. \ ntes 1900

"ids The complement fixation reaction has several times been found to be positive ^{43 216}

The provocation of specific lesions by irritation with phenol ²⁷ (not confirmed by Keim²¹⁸), by herpes lesions (Buschke after Langer,²¹⁶ Gjessing after Langer²¹⁵)



Fig 32 —Keratosis blennorrhagica without gonorrhea (From Lev r W F and Cawfo d G Marshall Arch Dermat 1944)

by inoculation with gonococcic pus and by maceration with wet dressings ²⁹ demonstrates the changed capacity to react which has developed under the influence of the infection. Possibly the blenitic keratosis are caused by inoculation of gonococci pus into an allergic skin which has acquired the peculiar keratogenic tendency.

²⁹ Guy and Jac B. Keratosis blennorrhagica Arch Dermat & Syph 21 703 704 1930
³⁰ Loh H and Ro nfeld H Klinisch und physiol. Untersuchungen über die Hyperkeratosen bei Gonorrhoe und Syphilis. In: Die Syphilis und ihre Arthropathien. Dtsch. Ztsch. 65 355-374 1922

³¹ Heron B B and Flett M H Keratosis blennorrhagica Arch Dermat & Syph 31 739 741 1935

³² Leander P and Pettersson H Keratosis blennorrhagica Lancet 1931 1116-1117

³³ Katsuj O Syphilisbefund der Keratosis blennorrhagica Jap J Dermat & Urol 32 98 103 1938

³⁴ Im H I Histogenese der Keratosis blennorrhagica Arch Dermat & Syph 9 403 1914

³⁵ Lo and R W Lett Keratosis blennorrhagica in Anschluss an Syphilis. In: Die Syphilis und ihre Arthropathien. Dtsch. Ztsch. 65 355-374 1922

The similarity of gonorrheic keratosis to arthropathic psoriasis may be considerable. However the history and presence of psoriasis, the vesicular primary lesions, the degree of keratosis, the distribution, the gonorrheic evidence, and a biopsy will secure the diagnosis. In psoriasis the arthritis follows the skin lesions while gonorrheic arthritis is more likely to precede the exanthema.²¹ Rupoid or tertiary syphilis may have to be ruled out.



Fig. 34.—Reiter's disease. Keratotic round lesion on glans penis. (Courtesy Dr. Sargent.)

The treatment is to heal the gonorrheic infection. The treatment with vaccines should be undertaken with the greatest caution to prevent exacerbations. Many authors stress the importance of proper nutrition and nursing of these patients who are often extremely weak, uncomfortable, emaciated and anemic. Vitamin A had good effect in one case after sulfathiazole had failed.²² As local measures, salicylic acid in plasters and ointments to remove the excessive keratotic masses should be applied. Great care should be taken to avoid irritation and maceration of normal skin in order to prevent provocation of new keratoses. Penicillin has in the only reported case of its application in keratosis blennorrhagica²³ failed to influence the course. It must be given further trial with high doses and prolonged treatment.

Polio myelitis

Rashes are not a characteristic of infantile paralysis. Red dermographism (tache cérébrale) is mentioned.²⁴

²¹ First in ■ *Differential Diagnosis of Acute Blennorrhagia and Psoriasis Arthropathica* Arch. Dermat. & Syph. 40: 559, 1930.

²² Stulsky F. M. *Erythroderma Blennorrhagicum* Am. J. Syph. Conor. & Ven. Dis. 29: 361, 1943.

²⁴ Wilson J. I. *Polio myelitis* Oxford Medicine vol. 3 New York 1940 Oxford Univ. Press pp. 107, 174.

Erysipelas

Singer¹⁶¹ observed various simple polymorphous or purpuric erythemas in the course of 25 per cent of his erysipelas cases. No substantial confirmation of this observation has become known.

Chancreoid

Lennhoff¹⁶⁷ reported a case of erythema nodosum like eruption in a case of ulcer molle. The secondary lesions ulcerated contained Ducrey Unna bacilli and were inoculable into the normal skin of the patient. Werther¹⁶⁸ succeeded in demonstrating the streptobacillus in the blood in a case of disseminated ulcera molia. Hematogenous infection from a soft chancre seems to be exceedingly rare since hardly any other well corroborated cases have become known.

Typhoid Fever

Typhoid fever is an endemic and epidemic contagious food or water borne disease caused by a gram negative motile bacillus *Eberthella typhi*. After an incubation period of from one to two weeks the disease starts insidiously with a slowly rising fever which reaches a high level with small morning remissions during the second week and diminishes by lysis during the third week or later. The pulse is much slower than the temperature would lead one to expect.

Abdominal and splenic tenderness and diarrhea with pea soup like stools are the most common symptoms. Delirium and severe general emaciation are other clinical features at the height of the disease.

Complications in almost every organ are known and the severity of the disease varies from symptomless carriers and walking typhoid to fatal cases. The outstanding post mortem finding is hyperplasia of Peyer's patches in the small and large bowel. The hyperplasia often results in ulceration which may lead to hemorrhage perforation and peritonitis. The spleen is enlarged and there is fatty degeneration of the liver.

Dermadromes—Typhoid fever has a characteristic exanthem known as *rose spots* or *roseola*. The rash consists of thin almost macular papules which blanch on pressure and measure hardly more than one half centimeter in diameter. They appear in small crops and last about three to five days. While the crops come and go about one to two dozen lesions are usually present from the end of the first week of the disease to the second or third week, rarely outlasting the fever. They almost always disappear without desquamation or pigmentation. In rare instances the rose spots are papular,^{169 170} hemorrhagic or vesicular.

¹ Lennhoff, K. Über ein Fall von knotigen v. reit roten hämatogenen N. tastasen an den Unt. rechen in b. i. w. i. h. m. Schank, r. Arch. f. Dermat. u. Syph. 121: 80-86 1911.

² Werther, August. Diss. mini. t. Ulcera molia bei welcher Streptobazillen aus dem Blute ge. Licht. wurde. Zbl. 37: 32 1931.

³ D. re. F. Cut. n. ou. Aff. ti. no. in. Va. i. us. Dis. as. Belt. J. Dermat. 18: 40 1906.

⁴ Rothmal, S. i. Zur K. n. n. t. s. s. e. t. e. n. e. Hauteruptionen b. i. typhösen Erkrankungen. Dermat. Wehnschr. 89: 981 983 1919.

The eruption is mostly concentrated on the abdomen the chest and the back and it usually appears first on these areas. Only in exceptionally dense eruptions does it invade the limbs and then the density decreases distally. The neck is rarely involved and the face remains free.⁵¹ The exanthem is a scanty one compared with those of other infections particularly in small children. The number of rose spots seems to vary in epidemics. An abundant rash is no indication of the severity of the infection.^{52 53} While some good observers failed to detect the exanthem in as high as 20 per cent,^{2 1} other authors (Eichorst after Miller⁵²) were able to detect rose spots in all the 2 000 cases of a series.

The pathological examination of the lesion shows a superficial rather thin, mainly leukocytic perivascular infiltrate in the upper corium which in the rare papular lesions invades the epidermis.^{54 55 56} The lack of plasma cells is striking.⁵⁷ Typhoid bacilli are in rare instances seen as metastatic deposits in the lymphatic spaces or between the cutis and the epidermis,⁵⁴ which may become separated within the small area of the rose spots. Frequently they can be cultured from the rose spots. However with the development of the blood culture this method has lost its diagnostic importance.⁵⁵

Hemorrhagic exanthems in typhoid are rare. H. Curschmann⁵¹ saw only 6 among 2 000 cases (all six patients died). The percentage was higher in other epidemics (McCrae after Miller⁵). Curschmann's⁵¹ observation of a small epidemic of typhoid with purpura is remarkable. A mother and six children all showed purpuric rashes. While their cases took a favorable course the father developed a hemorrhagic bullous eruption and died.⁵⁶ Roper⁵⁶ saw a similar case with extreme thrombopenia and leukopenia. The bullae appeared especially over the bony prominences.

Scarlatiniform morbilliform papular⁵⁷ varioliform⁵⁸ and other rashes may occur⁵⁶ (Da Costa after Dore⁵⁹) but they are rare. The absence of herpes is notable. Osler¹⁵ saw herpes only 20 times in 1 500 cases. Several clinicians feel that the presence of herpes should be a warning against a premature diagnosis of typhoid fever.

Miliaria crystallina (sudamina) is supposed to be more common than in other infections. The content of the clear vesicles is neutral or slightly acid. The blisters dry up and are destroyed before they become pustular. Miliaria appears mainly on the abdomen the chest and the thighs not on the face.⁶⁰ Urticaria is an occasional (0.3 per cent) complication. *Furunculosis* and *decubitus*

⁵¹Curschmann H. Der Unterleib typhus in Nothnagel's Spec. II Pathologie und Therapie vol III Vienna 1907 Alfred Hölder pp 108 119

⁵²Miller J. L. Typhoid Fever Oxford Medicine vol IV New York 1940 Oxford University Press pp 686 738

⁵³Poehlmann A. Urtica an Typhus und Paratyphus roseolen Arch f Dermat u Syph 121 384 452 1921

⁵⁴Fraenkel E. Ro cola typh sa und paratyphosa München med Wchnschr 9 325 3.3 1916

⁵⁵Baerthel in K. Abdominal Typhus Kohl und Wassermann's Handbuch der pathogenen Mikroorganismen vol III 2 p 1 III 1931

⁵⁶Röper K. Bullöse hämorrhagisch Dermatose bei Typhus München med Wchnschr 2 2036-2037 1931

⁵⁷Trusewitsch H. Typhus abdominalis mit atypischem Exanthem München med Wchnschr 72 2249 7 50 19 19

⁵⁸Cottchaik G. Variolaartiges Initialeranthem bei Typhus abdominalis München med Wchnschr 72 17 19 5

are common and troublesome. Curschmann⁵¹ described a type of bed sore which he often saw as a subcutaneous decubitus. Subcutaneous abscesses developed in the pressure areas and later opened forming multiple sinuses. Both furunculosis and decubitus can, to a certain extent be prevented by meticulous nursing care. Mottled sieve-like pigmentation and depigmentation has often been seen on the abdomen of children after typhoid fever.⁵²

Noma and other buccal ulcerations are very rare complications. Other ulcerations include *ulcus vulvae acutum*^{53 54} and a similar vulvar ulceration⁵⁵ with raised edges and a necrotic floor.

The tongue is furred especially at the height of the disease. The edges and the tip are often clean in contrast to the dorsum.

The face is flushed in the early period and dull and listless later.⁵⁶ Osler and Christian⁵⁶ emphasize the yellow color of the palms and soles and mention a very distinctive musty odor of the skin. The author has been unable to find more exact observations on this odor and in attending many patients with typhoid he has been unable to notice it.

Effluvium capillorum is very common after typhoid but only rarely does it reach extreme degrees with complete loss of the hair. *Beau's lines* of the nails are usually noticeable but shedding of the nails is rare.

The diagnosis of typhoid fever cannot rest upon the roseola alone but it constitutes a most valuable diagnostic criterion. For most practical purposes the paucity of the lesions, the complete blanching on pressure, the distribution on the trunk and especially the abdomen and the appearance of recurring crops will suffice to distinguish the roseola in typhoid from the rash in spotted typhus and other rickettsial diseases. In the rickettsioses the more abundant rash appears within two days in one outbreak, is usually hemorrhagic and the individual lesion is less neat and regular. There is more tendency to involve the extremities especially the more distal parts.⁵⁷

A negative Wassermann and lack of other syphilitic manifestations will rule out syphilitic roseola which is usually abundant and has larger individual lesions.

Paratyphoid Fever

The clinical picture in paratyphoid fever including the rash resembles typhoid fever. The rash was seen in about one half of the cases of an epidemic recently observed in England.⁵⁸

The *rose spots* in paratyphoid are more numerous than in typhoid. They occasionally cover even the hands and cheeks and desquamation occurs. Like the rose spots in typhoid fever the roseolae of paratyphoid are true bacterial

⁵¹ Henri Vass. J. Hauterkrankungen bei dem infantilen Abdominaltyphus. *Arch. Klin. u. Exp. Med.* 3: 4 1914 761-61.

⁵² Beilin O. Ulcus vulvae acutum in Typhoid Fever. *Arch. Dermat. & Syph.* 39: 59-91 1939.
⁵³ Zannini P. Ulcus vulvae acutum specificum et genitalium et ulcus vulvae acutum in Typhoid. *Poll. clinico (ser. prat.)* 11: 165 1691 1937.

⁵⁴ Polinso R. and Bait G. P. Typhoid With Buccal Ulcerations and Terminal Hematemesis. In *Child's Years Old*. *Mars. Ill.* 2: 692-693 1939.

⁵⁵ F. A. W. M. Glover. B. T. J. and Class V. Epiemic of Paratyphoid B Fever in Liverpool and District. *Brit. M. J.* 2: 369-371 1937.

metastases which contain bacilli sometimes even when the blood culture fails to demonstrate them. The pathology of the inflammatory reaction is similar to that of typhoid.²⁶⁶

Brucellosis (Undulant Fever)

Brucellosis (undulant fever) is a mild septicemia caused by bacteria of the genus *Brucella* which includes several pathogenic varieties. *Brucella melitensis* (Bruce) is found in goats, *Brucella abortus* (Bang) in cattle and *Brucella suis* (Traum) in swine. The microorganisms are very small pleomorphic gram negative nonmotile bacteria which are pathogenic for guinea pigs. The infection from goats is also known as Mediterranean or Malta fever, the infection from cattle as Bang's disease.

The routes of infection in man are the gastrointestinal tract and the skin. The incubation period varies from ten days to three weeks.²⁶⁷ The onset is gradual and the course of the fever varies. Most characteristic is the undulant type with repeated periods of persistently high temperature of ten to twenty days in duration. The general condition remains good, the paucity of objective signs is a remarkable clinical feature.^{268, 269}

The disease is rarely fatal but a great number of complications are known. They include heart and lung manifestations, arthritis, neuritis, meningitis, encephalitis, orchitis, mastitis, abortion and others. The laboratory diagnosis is based on agglutination, blood cultures which need two weeks to grow, and skin tests with brucella vaccines which are more reliable than serum agglutination.²⁶⁸ The cutaneous reactions can be used for differentiation of the various types.

Dermadromes—Skin manifestations are either ectogenous or hematogenous. The former occur at the site of contact with infectious material, particularly on the hands and forearms of veterinarians after delivery or manual removal of the placenta of Bang infected cows. These persons as a rule do not have a general Bang infection. They seem to become silently sensitized by repeated contacts. Thirty per cent of 325 Danish veterinarians,²⁷⁰ 10 per cent of the Swiss,²⁷¹ and 20 per cent of fifty veterinarians from Michigan²⁷² suffered from this allergy. In some cases warmth or itching and urticaria are felt during or very shortly after the contact. While this early reaction may be caused by other substances in the cattle serum or placenta,²⁶⁷ a second type of eruption is

²⁶⁶Frankel E. Über *Brucella paratyphosa* (Fraser) f. *Hysu* Infektionskrankh. 372:38, 1921.

²⁶⁷Haasdy A. V., Jordan C. F. and Bort I. H. Undulant Fever. Nat. Inst. Health Bull. No. 159, pp. 89, 1931.

²⁶⁸Robinson F. H. and Evans A. C. Chronic Brucellosis. J. A. M. A. 113: 201-206, 1939.

²⁶⁹Huddleston J. F. Brucellosis in Man and Animals. New York, 1943. Commonwealth Fund.

²⁷⁰Huddleston J. F. The Diagnosis and Control of Brucellosis. J. Oklahoma M. A. 35: 106-111, 1942.

²⁷¹Haxthausen H. and Thomson A. Brucella Ausschlag bei Tierärzten. Eine eigenartige Hautaffektion wahrscheinlich allergischer Natur hervorgerufen von *Bacillus abortus* (Bang). Arch. f. Dermat. & Syph. 162: 47-49, 1931.

²⁷²Schoch A. Skin Lesions in Brucellosis. P. axis 32: 51-59, 1943.

²⁷³Huddleston J. F. and Johnson H. W. Brucellosis. The Significance of Brucella Agglutins in the Blood of Veterinarians. J. A. M. A. 94: 1905-1907, 1930.

²⁷⁴Jadassohn W. Brucella-Bang-Ausschlag und Urticaria bei Tierärzten. Zbl. B. 5: 90.

papulopustular folliculitis which develops within two days is generally considered to be a specific reaction to *Brucella abortus* (Bang). The eruption is described by Huddleson as consisting of small discrete elevated, reddish widely separated follicular papules from 2 to 5 mm in diameter and 1 to 2 mm in elevation. The rash itches or burns intensely and may last as long as three or four weeks. Occasionally deep necrotic tubercled like lesions or erythema exudativum multiforme resembling forms are seen. Erythema brucellum, as the condition has been termed by Huddleson and Johnson is rarely followed by general brucellosis (Dietel and others after W Jadasohn²⁷). In some of the senescent persons, the attacks seem to become more acute with renewed exposures.²⁸

The systemic infection infrequently (11 per cent²⁹) produces rashes. Their incidence seems to differ in various countries.³⁰ They have been described as macular as resembling the roseola in typhoid³¹ or as (Curschmann after W Jadasohn) as star shaped vividly red or purple spots on the forearms neck and face in porcine cases³² morbilliform³³ scarlatiniform³⁴ (Grocco after Lustig and Vernoni) erythema exudativum multiforme like³⁵ as papular rashes involving cheeks neck and extensor surfaces³⁶ hemorrhagic bullous³⁷ varicelliform³⁸ and as resembling dermatitis herpetiformis and lasting over three years³⁹. The appearance in crops and the evanescent character of the rash are often emphasized. Aphthae in the mouth and a bad taste are sometimes noted early. Tonsillitis vesiculosa and uvulitis have been described⁴⁰ sometimes noted early occurs as a complication as it does in typhoid fever⁴¹. Ulcus vulvae acutum

Gabbi⁴² tried to differentiate the dermatomes of morbus Bruce (Malta fever) and morbus Bang. In the former he found the rash more often scarlatiniform in the latter more frequently vesicular and accompanied by bromidrosis. Profuse and exhausting sweats are one of the most unpleasant features of brucellosis.⁴³ Sudamina maceration and desquamation often follow the sweats⁴⁴.

In Iowa almost no rashes have been observed in a large number of cases (Personal communication to the author from Dr. Britz and Dr. Jordan, Des Moines, Iowa).

²⁷Gotttron H. Brucella-Ausaehtigung bei Tierärzten. Weikert Zbl 66 243 1938

²⁸Böhm F. K. Bang Infektion des Menschen. Ergbn d Hyg Bakter Immunol 1938

The ap 12 453 515 1937

²⁹Hummel J. Bang Disease in Man. Ztschr f Klin Fortbild 25 440-443 1939

³⁰Löffler W. Feb. undulans Bang der Menschen in Leipzig 1930. Curt habilitat.

³¹Nagel W. Übertragung der Banginfektion vom Schwein auf den Menschen. Zbl 61 970-975 1931

³²Rimbaud J. Jacobon M. and Alquier R. Indulgent Fever. G. necrosis of morbilliform Erythema in Melitococcosis. Arch Soc Med et Biol de Montp 11 2 647-648 19 7

³³Lustig A. and Vernoni G. Maltafeber. Rolle Kraus, Uhlenhuth Handb d. Infektiö. Pathog. 19 8 Gustav Fischer and Urban & Schwarzenberg pp 511 575

³⁴Arakelov C. Das Maltafeber in Asien. Zbl 61 970-975 1931

³⁵Curt H. Bang Infektion des Menschen. S. 472-473 in W. Nagel, J. A. Leber, Banginfektion beim Menschen. Dtsche Zbl 61 970-975 1931

³⁶W. Nagel, J. A. Leber, Banginfektion beim Menschen. Dtsche Zbl 61 970-975 1931

³⁷W. Nagel, J. A. Leber, Banginfektion beim Menschen. Dtsche Zbl 61 970-975 1931

³⁸W. Nagel, J. A. Leber, Banginfektion beim Menschen. Dtsche Zbl 61 970-975 1931

³⁹W. Nagel, J. A. Leber, Banginfektion beim Menschen. Dtsche Zbl 61 970-975 1931

⁴⁰W. Nagel, J. A. Leber, Banginfektion beim Menschen. Dtsche Zbl 61 970-975 1931

⁴¹W. Nagel, J. A. Leber, Banginfektion beim Menschen. Dtsche Zbl 61 970-975 1931

⁴²W. Nagel, J. A. Leber, Banginfektion beim Menschen. Dtsche Zbl 61 970-975 1931

Only few histological examinations of the lesions have been made and they refer to the contact eruptions or to cutaneous reactions with *Brucella melitensis* allergen. Perifollicular and perivascular infiltration with lymphocytes leukocytes and monocytes and occasionally an abscess have been observed.^{1 272 283}

Plague

In bubonic plague the primary skin lesion is caused by the bite of an infected rat flea. It may remain small and painless or it may develop into a pustule or even into a carbuncle followed by large suppurating bubos and septicemia. In the pulmonary form of plague a rapidly fatal septicemia follows or accompanies the severe pneumonia. The exciting organism is *Pasteurella pestis* which is found in the blood the sputum the urine and in many lesions especially in the bubonic pus. No other bacillus is known to occur in bubos in such large numbers.²⁸⁹

The disease is prevalent among several rodents. Occasional cases or small epidemics have often been seen in the western and southern United States. The data on the mortality and the value of serum and other treatment are extremely divergent. In many epidemics the mortality was higher than 80 per cent.

Dermadromes—Hemorrhagic inflammation is a characteristic feature of the infection. This is particularly true of the *plague carbuncle* which otherwise does not differ very much from any other carbuncle. The plague carbuncle starts as a small infiltrate with one or several blisters on its surface. These blisters may coalesce into a bulla with seropurulent and often hemorrhagic contents in which plague bacilli abound. The bleb disappears fast leaving a deep necrotic ulcer with raised edges on top of a rapidly growing cellulitis. A lymphangitic streak sometimes with bubonuli connects the carbuncle with the regional lymph nodes which turn into *bubos*. The development of the carbuncle may become arrested in any stage leaving hard cutaneous infiltrates which abound in bacilli and are known as *plague boils*.

The plague carbuncle is only occasionally the primary lesion of the plague infection. More often the carbuncle is a metastatic hematogenous or lymphogenous infection.²⁹¹ Sometimes the carbuncle develops at the site of infection at a later time than the bubo. The incidence of carbuncles varies in the epidemics from 10 to 15 per cent being a fair average.²⁹¹ Araujo²⁹² in a recent report found skin manifestations in only 7 per cent. Other skin manifestations are erythema pustules vesicles bullae and hemorrhagic lesions. The latter are supposed to be so common and their appearance so ominous that from them originated the name of black death as the disease was called during the great European outbreaks in the Middle Ages. Such large fulminant hemorrhagic skin lesions have

¹ Cershi I and Black W C. Histology of Cutaneous Reaction to *Brucella Melitensis* Antigen. Arch Path 27 307 31 1939

² Lloyd B J. Personal Experience with Bubonic Plague. J Trop Med 41 110 123 1941

³ Muller H F and Poch R. Die Infektionskrankheiten des Menschen und Tiere. 11. Aufl. 1900. Alfred Hield.

⁴ Araujo. Hauterkrankungen bei Pest. Statistisches Klinisch-pathologisches Bra 11 med 25 1-4 19 1 7bl 4 1-2

not been noticed in the large plague epidemics of modern times. However petechial rashes occur which contain bacilli and therefore are a true metastatic infection (Albrecht and Ghon after Muller and Poch⁹¹). Hemorrhagic streaks around the navel and in other sites have been recorded²⁹¹.

A rare occurrence are the papulopustular generalized dense varioliform exanthems⁹³.

Tularemia

Tularemia is named after the California county of Tulare where it was first observed among squirrels by McCoy²⁹⁴. In man it is usually acquired by the handling especially skinning of wild rabbits, hares, squirrels and other rodents or by eating the insufficiently cooked meat from them. It has been shown to be carried by ticks^{93, 296}, bedbugs²⁹⁷ and other insects⁹³. Laboratory infections have occurred in a considerable number although no contagion from man to man has become known except for one case of a physician at an autopsy (Weilbacher and Moss after Robert²⁹⁹).

The cause is a small pleomorphic gram negative bacterium *Pasteurella tularensis* which seems to be able to penetrate the unbroken skin as well as the mucosa. The incubation period is most often four days but it varies considerably. In traumatic infections the first symptoms at the site of the injury may develop after a few hours^{300, 301}. Fever may break out suddenly before any other symptoms even before the primary lesion appears³⁰. This indicates the early dissemination of the infection. If the infection begins in the skin which is by far the most common way a primary lesion develops and the disease spreads along the lymphatics. The regional lymphatic vessels become indurated, small nodules or bubonuli appear along them and bubos develop which may reach large size and may suppurate.

If the infection occurs in the conjunctival sac (1 per cent Hurst after Tassman³⁰², 3 per cent after Pullen and Stuart³⁰³, 12 per cent Vria after Robert²⁹⁹) or in the tonsils characteristic clinical pictures of long lasting lid edema and suppurative lymphadenitis develop. The typhoid resembling type without apparent portal of infection is very rare. It has been seen in several laboratory infections. The severity of the infection varies from mild ambulatory cases with little fever and no internal complications to illnesses of many months duration sometimes with a fatal outcome. The mortality in the United States amounted

⁹¹ Teissier P, Reilly J, Cambes les and Cathala. Form exanthématique la peste bubon qu Bull et mém ⁴ e mérid H hôp de Par 49 8 4 1921 192

²⁹⁴ McCoy C W and Chapin C W. Tularemia. Bull 43 Hyg Lab C. & P H 8 1911

²⁹⁶ Davis G E, Philip C B and Park R R. Isolation from the Rocky Mountain Wood Tick of Bacterium Tularensis. Am J Hyg 19 449-456 1934

²⁹⁷ Byfield C A, Breslow L, Croft H R Jr and Hershey N J. Tick Borne Tularemia. JAMA 127 191 196 1945

²⁹⁹ Bogenko V. Bedbugs as Carriers of Tularemia. Vestnik mlk 14 436 1915 Zbl B 211

³⁰⁰ Miller H E and Tausig L H. Tularemia. Arch Dermat & Syph 19 378 390 1929

³⁰¹ Robert F. Tularemia. Rev of literature. Dermatologica 60 98-107 1939

³⁰² Pullen R L and Stuart B M. Tularemia. 5 Cases. JAMA 123 47 1939

³⁰³ Stuart B M. Tularemia and Pneumonia. Am J M & C 201 3 191

⁹³ Betch O. Die Bionorm und Tularemia. Zentralbl f Chir 67 1 125 1940

⁹³ Tassman J. Eye Manifestation of Internal Diseases. St Louis 1941 Th C & Mosby Company

to 48 per cent among 7 077 cases reported from 1924 to 1936³⁰⁴ The autopsy findings often resembled those of tuberculosis^{30 305} There are milium gray foci in the enlarged spleen and less often in the liver and in the lungs which may show pneumonia or abscess The microscopic picture of the lymph nodes and the subcutaneous nodules is that of an infectious granuloma³⁰⁶ with epithelioid cells lymphocytes and giant cells of the Langhans type creating a great similarity to tuberculosis³⁰⁷

The microorganism can be isolated from the blood of the patient by inoculation into guinea pigs and by culture This however is hardly possible after the first two weeks³⁰⁸ and it has rarely been accomplished from an open lesion³⁰⁹ Agglutination in serum dilutions above 1 80 is considered diagnostic³¹⁰ Skin allergy to tularemia³¹¹ develops as early as four days after infection or even sooner³¹² The intracutaneous test with 0.02 or 0.05 c.c. of a bacterial suspension is read after forty eight hours The disease seems to leave the patients immune

The treatment is symptomatic The value of antiserum derived from goats³¹³ which has been found effective in reducing the severity and duration of the disease³⁰⁰ needs confirmation The beneficial effect of the sulfonamides is not generally confirmed³¹⁴ Streptomycin is now considered to be the drug of choice

Dermatomes—The primary lesion may occur almost anywhere on the skin It may be single or there may be multiple lesions The primary lesion appears after a period of about one week when general dissemination has already manifested itself by fever and malaise Even the regional lymph nodes may become enlarged and tender before the appearance of the primary lesion The initial lesion is a papule the center of which soon becomes depressed and necrotic forming a punched out ulcer with raised edges This ulcer is painful and defies therapy but after several weeks it heals spontaneously³⁰⁸ The early lesions of tularemia may imitate syphilis anthrax felon or other conditions Due to the lymphatic chain of nodules or abscesses the picture may closely resemble sporotrichosis or primary inoculation tuberculosis^{38 315}

In the primary stage the diagnosis often can be secured only by the intracutaneous test

The bubonuli and lymph nodes may become tender adhere to the skin and ulcerate In one case reported by Blackford and Smith (quoted after Hitch

¹ Cumming H. A. Tularemia Bull. Office Internat. d'hyg. Pub. 29 12 1937

² Gundry L. P. and Warrar C. C. Fatal Tularemia 15 Autopsies Ann. Int. M. d. 7 837 85 1934

³ Lawless I. H. Tularemia Arch. Dermat. & Syph. 44 147 160 1941

⁴ Cuy W. H. and Jacob F. M. Tularemia Arch. Dermat. & Syph. 44 909 1931

⁵ Hitch T. M. and Smith D. C. Cutaneous Manifestations of Tularemia Arch. Dermat. & Syph. 38 859 876 1934

⁶ Thornton E. W. Tularemia Cutaneous Manifestations Arch. Dermat. & Syph. 16 170 184 1927

⁷ Pasteback J. C. Tularemia Inguinal Buboes Following Tick Bite J. A. M. A. 112 1814 1817 1939

⁸ Fahay L. Tularemia Failure Diagnosis by Intracutaneous Reaction J. Infect. Dis. 51 286 1933

⁹ Larson C. W. Interesting Case of Tularemia Tri-State M. J. 11 2704-2714 1911

¹⁰ Fahay L. Tularemia Treated by a New Specific Antiserum Am. J. M. Sc. 187 23 745 1934

¹¹ Waring F. H. Tularemia 10 Cases J. Oklahoma M. A. 25 103 106 1941

¹² Smith H. Tularemia Resembling Sporotrichosis Arch. Dermat. & Syph. 11 918 91 1929

and Smith³⁰⁸) fungating growths developed out of such bubonuli. The histological structure of the subcutaneous nodules is definitely tubercloid.

Generalized *eruptions* are a feature of the disease but they occur only in a fraction of the cases (8 per cent after Pullen and Stuart³⁰⁹) and are not characterized by any specific morphology. Hitch and Smith³⁰⁸ surveyed forty eight cases of secondary eruption in tularemia. They demonstrated that eruptions occur in all types of the disease most often in the second week, and that the average duration is three weeks. However great deviation of the average figures is



Fig. 35.—Tularemia. Erythema nodosum multiforme resembling eruption on fifteenth day of the disease. (From Hitch, J. M. and Smith, Dudley C. Arch. Dermat. 1935.)



Fig. 36.—Tularemia. Papular rash. (Courtesy Dr. Walter M. Simpson from Sutton and Sutton. Diseases of the Skin. The C. V. Mosby Company.)

frequently observed. Pleomorphism is a characteristic feature. The most commonly encountered morphologic type was the papular eruption which was seen in approximately one half of the eruptive cases. Less common are macules, pustules, vesicles, wheals, nodules, ulcerations, and transitional forms. The rashes often gave the impression of erythema multiforme, sometimes with herpes iris lesions. The eruptions were generalized or they involved only a part of the body, mostly the upper trunk and the arms, especially on the side of the primary lesion. In ophthalmic cases, a facial eruption appeared on the side of the infected eye. The eruptive cases did not differ from the noneruptive ones with regard to incubation period or agglutination titer. The histological examination did not reveal changes other than one might expect, that is, edema and perivascular lymphocytic and fibroblastic infiltration. The common appearance of the rashes after the period of bacteremia and fever supports the conception of the toxic rather than infectious nature of the secondary rashes in tularemia.

The prognosis of the secondary rashes is good; the treatment is symptomatic.



Fig. 37.—Primary lesion of tularemia and lymphangitis in the left orbit. (Courtesy Dr. Walter M. Simpson from Sutton and Sutton, *Diseases of the Skin*, The C. V. Mosby Company.)

Erythema Arthriticum Epidemicum, Ratbite Fever or Haverhill Fever

Erythema arthriticum epidemicum, ratbite fever, Haverhill fever*—none of these three names is correct. The disease is not always epidemic, does not always follow a rat bite, and Haverhill, Mass., is neither the only nor the first place where it was observed. *Erythema arthriticum* would be a good name, but the term Haverhill fever has become established.

The disease is an acute infection which usually follows a rat bite. It should not be confused with sodoku, which is also transmitted by rat bites. While the ratbite cases occur sporadically,^{1,2} a milk-borne epidemic with eighty-six cases

* Bibliography of the ratbite fever: Brown, T. M. and Sundersaker, T. G. Bull. Johns Hopkins Hosp. 70: 61-80, 1942.

¹ Farr, B. F., Lee, H. C. H. and Vogelt, T. Haverhill, Mass., Calif. With Review of Literature. Arch. Int. Med. 65: 1-14, 1939.

was observed in Haverhill Mass. in 1926^{217 218} and another milk borne—not quite verified—outbreak of 600 cases at Chester Pa. (Armstrong and H. Wood after Place and Sutton²¹⁹). The epidemic and sporadic forms are caused by the nonmotile pleomorphic gram negative and nonacid fast *Streptobacillus moniliformis* (Haverhillia multiformis)²¹⁸ which during the fever can be cultured from the blood of the patient. Vice die from the disease forty eight hours after intra peritoneal injection of blood.

About three days after the infecting bite of rats who often harbor the microorganism in their pharynx the disease starts quite suddenly with malaise headache chill and high fever. A rash and acute polyarthritis develop early and heal after several days. There is a leukocytosis of over 12 000. The spleen is not enlarged. There were no fatalities in the Haverhill epidemic. A rash was observed in 94 per cent of the Haverhill cases which appeared during the first week most often between the second and fifth days. It involved predominantly the lateral and distal extensor surfaces of the extremities rarely the trunk and face. There is sometimes accentuation around the joints²¹⁸. The exanthem has been described as a maculopapular rubelliform or morbilliform vividly red eruption with the efflorescences being about 3 to 5 mm. in size²⁰. In some cases the exanthem had the characteristics of erythema exudativum multiforme (Leviditi Nicolau and Poincloux after Farrel and associates²¹⁶). The rash usually fades after one week with little desquamation or pigmentation. The exanthem may reappear with new paroxysms of the fever. Then it is likely to be more confluent²⁰. A hemorrhagic tendency can be demonstrated by a positive tourniquet test and by pin point hemorrhages in the center of the lesions.

In the cases studied by Allbritten Sheely and Telfers²⁰ tender purpuric nodules with yellow nonsuppurative depressed centers resembling those seen in subacute bacterial endocarditis appeared around the finger tips. They probably are metastatic embolic foci. Lymphadenopathy in relation to the site of the bite is rare²⁰.

The diagnosis rests on the history of a rat bite and the laboratory findings. Agglutination tests are known. A cutaneous reaction to suspensions of killed streptobacilli was present in 83 per cent of the Haverhill patients tested late in convalescence. It seems important to compare the symptomatology of Haverhill fever and that of sodoku the other ratbite disease which may occasionally cause a syndrome quite indistinguishable from Haverhill fever²¹. Usually sodoku (see under sodoku) presents a chancreiform induration at the bitten area which is followed by lymphangitis. Arthritis is rare. The causative organisms of both diseases are penicillin sensitive (Wheeler after Fleming^{21a}).

²¹⁷Place F. H. Sutton I. E. and Williams R. O. Frystma Arthritis Epithelium Iridiary R. port. Boston M. & J. 194 5- 87 19 6

²¹⁸Place F. H. and Sutton I. E. Haverhill Fever Arch. Int. Med. 61 1 1934

Larke E. Jr. and Hindon N. P. Haverhill Fever Am. J. Path. 2 357 19 6

²¹⁹Allbritten F. F. Sheely R. F. and Telfers W. A. Haverhill Multiformal Exanthema Relationship to Haverhill and Ratbite Fever J. A. M. A. 114 370- 363 1930

Hillborn T. M. and Nunneker J. C. Ratbite Fever Review of American Cases Bull. Johns Hopkins Hosp. 76 61 1942

Glanders (Malleus)

Glanders (malleus) occurs predominantly and in large epizootics among horses from which most of the rare human cases originate. A number of laboratory infections have become known.² The disease which has an incubation period of from three to five days is caused by the pleomorphic nonmotile bacillus *Malleomyces mallei*. The germ enters the human body through the skin or through the mucosa possibly without a wound. From a primary lesion the disease spreads and frequently becomes generalized, taking an acute or irregularly relapsing chronic course of unfavorable prognosis. Specific lesions may occur in any organ but there is a definite cutaneous and mucosal affinity. The predominantly lymphangitic form is sometimes called farcy while the term glanders is often used for those cases in which the mucosal especially the rhinitic involvement dominates the picture. Not very long ago the two forms were believed to be different entities. The specific malleal lesions are granuloma which resemble tuberculosis in many ways.

The diagnosis rests on a history of contact with horses or mules, the unusual clinical picture, the microscopic and cultural evidence of *Malleomyces mallei*, the intraperitoneal inoculation into the male guinea pig followed by the specific inflammation of the testes and various serological and allergic tests among which the complement fixation, the ophthalmic and the intracutaneous tests have been used in man.

Dermadromes—The primary lesion which has been most often observed on the hands and arms, the face and the conjunctiva is a furuncle like infiltration which soon breaks down in the center and forms an ulcer with jagged raised livid and infiltrated edges and a necrotic floor with edematous and erythematous surroundings.^{3,4} The lesion may reach dollar size but it finally heals spontaneously. In some cases it fails to develop so that lymphangitis appears as the first cutaneous symptom. Lymphangitis without noticeable lymphadenitis is a peculiar feature of malleus in human beings.^{3,5} The wire or pencil like lymphatics are palpable along the extremity and small bubonuli (buds) develop alongside the vessels. This type of lymphangitis resembles sporotrichosis or tuberculosis. Sinuses sieve-like perforations, ulcers and scars may develop. In rare instances the disease becomes chronic in this stage. The primary lesion of the oral or nasal mucosa is an ulcer similar to that of the skin.

General systemic infection follows the majority of the primary lesions. The period after which systemic symptoms appear may be a few days to many weeks or months. The skin manifestations of the systemic infection have a predilection for the nose and face. These secondary malleids appear in crops and show great differences in severity, grouping and number. The exanthem usually starts as a roseola. The maculae which in rare instances are purpuric become papular, papulopustular and later ulcerative. They are occasionally bullous or composed

¹Roos J. W. Acute Glanders. *Can. Med. Assoc. J.* 2: 372-374, 1919. Zbl

29

³Birnbaum H. and Gottrohn H. Rotz (Malleus). *Hanb. d. H. u. L.* 3: 355-356, 1919.

of concentric rings^{2 4} resembling erythema multiforme. These ulcers may by infiltration of the surroundings and by coalescence grow to larger plaques which may also develop from cutaneous or subcutaneous nodules. Breaking down of nodules or plaques may cause deep destruction of the muscles and tendons and even affect the joints.^{2 2} Destructive and suppurative lesions in and around the nose may cause a peculiar swelling and erythema of the nose which has been termed by de Balogh³ who reported eight cases potato nose. This author describes nonsuppurative livid nodules in the face as typical secondary lesions.

The histology of the fully developed lesions shows granulation tissue composed predominantly of leukocytes and to a lesser degree of epithelioid plasma and mast cells. There is a pronounced necrotic tendency. Karyorrhexis is a feature and bacilli may occur in large numbers.

Sporotrichosis, tuberculosis and pyogenic lymphangitis must be considered in the lymphangitic period and syphilis and mycosis fungoides in the later systemic stages. The common concentration around the nose and the necrotic tendency of the granuloma support the clinical diagnosis of malleus. However, considering the rarity of human glanders and the many varieties of its course all laboratory methods must be employed.

Generalized glanders in man is almost without exception a fatal disease. Chronic localized malleus heals spontaneously in about 50 per cent of the cases (Bollinger after Bierbaum and Gottron^{2 3}). No specific treatment is known.

Cholera Asiatica

Cholera asiatica is an acute, often epidemic infection caused by the *Vibrio comma* (Koch). In its severest fulminating form the disease may run a fatal course in from three to four hours, but less severe forms are well known. The outstanding symptoms are excessive watery diarrhea, dehydration and circulatory collapse.

Dermadromes—The skin is described as pale or cyanotic, even livid, covered with sweat, wrinkled and withered. Urea frost has often been seen covering such dehydrated patients. In fact, this sign was described in cholera long before its association with uremia was noted (Schottin after Chargin and Keil^{2 4}). In cholera there is a pronounced tendency to necroses and decubiti.^{2 7} Exanthems are infrequent.

The older literature contains a number of references. Liebermeister^{2 8} in a monograph written after the great epidemic of 17,000 cases in Hamburg, Germany, in 1892, denied the existence of a specific exanthem at the height of the disease. In the early stages of recovery cyanotic spots may remain as remnants

¹ Weing A. Ueber den Fall von akutem Rotz Buns Beitr Klin Chl 125 433-443 19
² Balogh F. d. Skin Lesions in Human Glanders Virch Arch Internat Congr Dermat 2 427-431 1936

³ Chargin L. a. Keil H. H. Skin Disease in Nonsurgical Real Disease Arch Dermat & Syph 26 314-315 1931

⁴ Elias H. and Doe R. Cholera Asiatica Handbuch d. inneren Medizin Berlin 19 5 Julius Springer

⁵ Liebermeister F. Cholera Asiatica und Cholera nostras Nothnagel's Specielle Pathologie und Therapie VI a 1506 Alfred Hield

of the collapse of circulation during the attack. Roseola and other erythemas especially of the erythema multiforme type papules vesicles urticaria and petechiae have occasionally been seen but the specific character of these rashes has not been demonstrated. Some may have been drug eruptions.³⁷

Whooping Cough

During the characteristic attacks the glottis is temporarily closed and at the termination of the spell it is opened for a long drawn crowing inspiration.³⁸ The disease is caused by a small bacillus with accentuated poles discovered by Bordet and Gengou.

Dermadromes—The repeated severe coughing spells frequently produce some puffiness around the eyes especially of the upper lids together with slight chemosis. This is known as the *whooping cough face*. Petechiae which are quite rare in the skin occur more frequently in the mucosae especially in the conjunctivae of young children. Both bulbar conjunctivae may be deep red a terrifying but harmless sign.

The vesicles of a *varicella exanthem* coinciding with whooping cough may become hemorrhagic due to the coughing bouts. This is especially true of the vesicles in the area drained by the upper vena cava.³⁹ The violent fluctuations of vascular pressure during the cough and possibly the infectious and toxic damage to the capillaries may prepare the rhexis of the capillaries.

Cutaneous *emphysema* is a rare but dangerous complication of whooping cough. It is caused by the rupture of alveolar vesicles due to the high intra pulmonary pressure. From the ruptured lung the air is pressed under the pleura which on autopsy has been seen to be separated from the lung. The air follows the mediastinum and finally reaches the skin of the neck or chest.

A well known complication of whooping cough is the shallow *ulceration of the frenulum linguae*. It results from injury and irritation of the frenulum caused during the coughing by the incisor teeth or in the absence of teeth by the hard lower jaw.

Diphtheria

Exanthems indicative of generalized diphtheric infection are rare. Some rashes have been interpreted as initial exanthems since they occurred during the first day.⁴⁰

Purpuric morbilliform scarlatiniform papular and vesicular eruptions resembling erythema nodosum and multiforme and even typhoidlike rose spots have been described. Allowance must be made for drug eruptions true scarlet fever⁴¹ and serum exanthems.

Herpes seems to be rarer than in many other infectious diseases. The herpes vesicles may contain bacilli (Rall after Biberstein⁴²).

³⁷ Knoepf Imacher W. Whooping Cough Pfandner and Blossmann. The Diseases of Children vol. III Philadelphia 1935 J. B. Lippincott Company pp. 363-351.

³⁸ Bibb et al. II. Die Diphtherie der Haut. Handb. d. H. u. Ch. 9 I. 145-19, 1930.

³⁹ Brua P. Esant malscarlattiniforme i rot razi in corso d'inf. diff. It. Scrittura dedicata a Carlo Comi. Riv. di clin. e diet. 27 4 6-434 1939.

Panniculitis (Weber-Christian Disease)

Twenty eight cases of a syndrome of relapsing febrile nodular nonsuppurative panniculitis (Weber Christian disease) have been reported since 1892³² There are crops of cutaneous and subcutaneous painless or tender nodules mostly on the thighs and arms but also on the trunk and accompanied by fever The lesions are the expression of an inflammatory process which results in atrophy of the subcutaneous fat producing in the skin lasting depressions of a varying depth and width Fever is a constant symptom Two cases were fatal The etiology and even the clinical entity itself are still controversial Focal infection tuberculosis eruptions from iodine or bromides and other causes have been considered³³)

³²Pfeifer V Ueber einen Fall von herdw eise r Atrophie des subcutanen Fettgewebes Deutsches Arch f klin Med 60 439 449 1892

³³La kin V P De Sanctis A C and Magalis A E Panniculitis—Review of Literature Am J Dis Child 67 1 0 12 1944

CHAPTER IV

SYSTEMIC INFECTIONS

Influenza

Influenza is almost certainly caused by at least three different types of virus³³⁴ now called A, B and C but is usually complicated by the secondary invasion of various bacilli especially the Pfeiffer bacillus the pneumococcus and the pyogenic cocci. Sporadic cases occur although epidemics and pandemics are characteristic of the disease. Influenza is very contagious. The incubation period is short about two days. The onset is quite sudden sometimes with marked catarrhal symptoms or sore throat. The fever is irregular and chills and remissions are common. The respiratory tract in its full length is inflamed bronchitis and pneumonia are serious complications which in 1918 caused most of the deaths.³³⁵ Prostration is often marked and not explained by the temperature alone. Gastrointestinal symptoms and sometimes severe and irreversible lesions of the nervous system may in a small minority of cases dominate the picture. Many other complications are known. Mild leukopenia is common before secondary infection supervenes.

The post mortem findings concern chiefly the respiratory tract.

The mortality varies from 15 to 60 per cent depending on the character of the epidemic³³⁶ although exact figures are not available. In 1918-1919 at the time of the last influenza pandemic there were 550,000 deaths in the United States in excess of the normal expectancy. No specific treatment has been discovered as yet.

Dermadromes—The skin manifestations are neither impressive nor of diagnostic importance. They rarely influence the course or cure suffering to the patient.³³⁷ The incidence of skin and oral symptoms given by various authors varies from 1 to 20 per cent. However such percentages are of little value in a disease which in many cases is difficult to differentiate from other common respiratory infections.

During the febrile period *herpes simplex* is common and sometimes develops even after the temperature has returned to normal. The appearance of herpes does not seem to depend on the respiratory involvement.³³⁷

Exanthems of great variability have often been noticed usually in the early stages of the infection. These skin eruptions are most often macular³³⁸ or mor-

³³⁴ Hoorfall, F. J. Jr. *Present Status of Influenza* JAMA 120: 284, 57, 1934.

³³⁵ Top F. H. *Communicable Diseases* St. Louis 1931. The C. V. Mosby Company.

³³⁶ Schütz H. *Dermatologie und Gynäkologie* Med. Welt 13: 1,006 1,010 1939.

³³⁷ Schumacher C. and Moncorpe C. *Haut- und Geschlechtskrankheiten* 711 16.

³³⁸ 94 102.

³³⁹ Freund. *Crippexanth* = 7bl 23 6.

billiform³³⁹ less frequently scarlatiniform³⁴⁰. Besides these main types urticarial, vivid red papular³⁴¹, purpuric and spotted typhuslike rashes have been recorded. There are combinations of macular and hemorrhagic lesions³⁴². The serious prognostic significance of purpuric rashes is often emphasized. Erythema nodosum and erythema exudativum multiforme³⁴³ have been observed in a considerable number of cases.

Most of the influenza rashes are very transitory^{339, 344}. The difficulty in differentiation from measles, scarlet fever and other exanthematic diseases is often great. A carefully taken history of contacts and previous diseases, consideration of the incubation period and negative results of the diagnostic procedures used in other infections will usually help to overcome the difficulties. In sporadic cases the diagnosis may be made only after further observation of the course. Jordan³⁴⁴ emphasizes the lack of adenopathy as a criterion against rubella.



Fig. 38.—Virus tongue in influenza. The tongue is large, flabby and shows dental impressions. (Courtesy Dr. Max Fox.)

In the oral mucosa circumscribed erythema of the soft palate and the posterior tongue and a buccal exanthem not unlike Koplik's spots in measles are common³³⁷. A flabby, slightly edematous tongue showing marginal impressions of the teeth (virus tongue) is often considered characteristic of influenza and other virus diseases. The pharyngeal involvement may occasionally become severe. Follicular tonsillitis, pseudomembranes of the pharynx and small ulcerations of the mucosa may even lead to glottic edema.

³³⁹Opt. H. Gripp exanthem. *Intern. ärztl. Praxis* 6: 154, 16, 1935.

³⁴⁰Ösch. H. Exanthem bei Grippe. *in F. Krankheiten. Wien. med. Wchnschr.* 78: 95, 19, 8.

³⁴¹Dessy. I. Sulle manifestazioni papulari cutanee nella influenza. *Riforma med.* 53: 815-819, 1937.

³⁴²Leicht. nt. H. B. and Schöber. W. Gripp exanthema. *in Wchnschr.* 3: 10, 9, 103, 19, 4.

³⁴³Oppenheim. Gripp exanthema. *Zbl.* 38: 743.

³⁴⁴Jordan. A. Über Grippeausschlag. *Dermat. Wchnschr.* 91: 1011-1014, 1939.

Following the acute period erysipelas of the face has often been observed especially in the older epidemics. Other common cutaneous sequelae are furunculosis and herpes zoster. Symmetric gangrene of the extremities is an exceedingly rare event³⁴⁵.

Alopecia diffusa was a common dermatome during the epidemic of 1918. The shedding of the hair after influenza was often troublesome although the hair usually grew back. Beau's lines of the nails were often observed. The dermatomes of influenzal encephalitis will be discussed in Chapter XXXIX.

Measles

It is generally agreed that measles is caused by a filtrable virus which lately has been cultured in the chick embryo³⁴⁷ (Kunert and Wenkebach after Rietschel³⁴⁶) and successfully inoculated into the child after several passages.



Fig. 39 — Measles fifth day. Exanthem and conjunctivitis. (Courtesy Dr. Mac Fox.)

The disease is highly contagious among persons who have not had much exposure to the virus and therefore is predominantly a child's disease. Measles

³⁴⁵Mott, A. Gangrène aiguë symétrique de extrémités post gripale. *Gaz. méd. de France* 46: 649-650, 1939.

³⁴⁶Rietschel, H. Measles. *Review of Literature*. *Monatsschr. f. Kinderh.* 33: 31-35, 1911.

³⁴⁷Rake, C. and Schaffer, M. F. Studies of Measles. Use of Chorio-Allantois of Developing Chicken Embryo. *J. Immunol.* 38: 177, 1940.

is most contagious about twenty four hours before the eruption. With the appearance of the exanthem the infectivity decreases rapidly and is nil at the time of desquamation. The infectious agent is present in the respiratory tract and in the blood and it has also been demonstrated in artificial blisters of the skin. Lifelong specific immunity after measles is the rule, true reinfection being extremely rare.

The first catarrhal symptoms appear not too suddenly after an incubation period of about ten days. Headache, anorexia, conjunctivitis and coryza, sometimes with nosebleed, cough, vomiting and sudden fever are the common prodromal symptoms. On the first day the lower lids may be slightly puffy and a fairly definite erythematous transverse line appears across the conjunctival surface of the lower eyelid about a third of the distance from the lid margin to the fornix (Stimson after Sobel in Mackee and Cipollaro¹⁴⁴).

On the second day of the prodromal stage a few (from six to twenty) pin point sized white spots, often surrounded by a bright red, at first narrow but soon widening areola, appear on the buccal and later often on the labial mucosa. This prodromal mucosal eruption which is commonly known as Koplik's spots is of great diagnostic importance since it hardly occurs in other diseases and it can be seen in about 90 per cent of the measles cases preceding the outbreak of the exanthem. The Koplik spots vanish when the rash appears and are soon followed by an enanthem of dark red spots of pin head to lentil size which may coalesce into large spots scattered over the soft palate and later over greater areas. Koplik's spots may be absent in the measles of small children.¹⁴⁵

The temperature usually drops on the second day only to rise again during the next two days. Between the third and fifth days (two weeks after the infection) the rash appears. The disease reaches its height around the fifth day and from that time on the symptoms are eased. On the seventh or eighth day after the full development of the rash the temperature gradually becomes normal, the rash fades and the catarrhal symptoms are no longer annoying. Recovery follows gradually. Cervical adenopathy is common but is mild and rarely leads to abscesses.

The clinical picture is dominated by the rash and the intense catarrhal involvement of the mucous membranes, particularly of the respiratory tract and of the eyes. There is leukopenia at the height of the rash, mainly caused by a drop in the lymphocytes.

The list of possible complications is long but fortunately the overwhelming majority of the patients recover uneventfully.

Dermadromes—Pale scarlatiniform or macular *premonitory rashes* are rare and very fleeting^{146 147 148} and may disappear before the outbreak of the measles rash.

¹⁴⁴Stimson, E. Daskritische Dreitagefieber exanthematoides (Exanthema subitum). Festschrift für Kinderh. 29: 65-89, 1916.

¹⁴⁵Soucek, A. Nasenbeobachtungen prodromales Exanthem. Wochenschr. 23: 1849, 1917.

¹⁴⁶Wieland, G. Ueber fibroblasten-scarlatiniforme Rash bei Masern. Monatsschr. f. Kinderh. 42: 48-49, 1919.

¹⁴⁷Nöthen, J. Vor exanthem bei Masern. Jahrb. f. Kinderh. 88: 211, 1919.

The *exanthem*²⁵¹ (Von Pirquet in Von Groer²⁵²) starts with pale pink spots from 1 to 5 mm in diameter. Intense itching may accompany the eruption. The spots are seen clearly first on the scalp behind the ears and between the shoulder blades, less distinctly around the mouth and nose and in front of the ears. The cheeks offer a certain resistance but are soon invaded also. On the second day a dense exanthem appears on the back and although less pronounced on the chest, abdomen and mesial aspects of the arms. On the third and fourth days the development is completed with the invasion of the legs. The emphasis



Fig. 40.—Measles (courtesy Dr. Ma. Fo.)

is on the head, trunk, shoulders and anterior surfaces of the arms and thighs. On the fifth day the appearance of new lesions usually stops. With the return to normal temperature the spots fade in the order of their appearance, leaving a pigmentation which is sometimes quite pronounced on the forehead. There is a superficial branny desquamation which usually starts on the face from two to five days after the appearance of the exanthem.²⁵³

The first lesions are follicular spots or slightly palpable papules surrounded by an anemic halo. They grow quickly in size and number and become confluent, but the original follicular papular character can still be recognized within the larger bright red spots of the developed exanthem. There is a great variability

²⁵¹ Von Groer, F. *Measles*. Pfaunder and Schloswann. *Diagnoses of Children*, v. 1. Philadelphia, 1935. J. B. Lippincott Company, pp. 170-21.

²⁵² Kolly, E. *Acute Exanthem*. *Handbuch der inneren Medizin*, vol. 1. Berlin, 1935. Julius Springer.

²⁵³ Reuland, A. *Erbir Hautschuppung nach Masern*. *Jahrb. F. Kinderh.* 115: 20-24, 1917.

in the exanthems with regard to size of lesions density and tendency to remain discrete or become more confluent At its height the eruption is blotchy and dusky red Miliary vesicles are quite common on the follicular papules Increased seborrheic activity makes the skin feel greasy The tourniquet test is usually positive

While the exanthems may vary great similarities of the rash in siblings as well as in individual epidemics have been observed indicating the power of constitutional and microbic factors

The histopathology of the measles³⁵⁵ exanthem is characterized by vacuolization in the epidermis and a perivascular predominantly lymphocytic infiltrate in the papillary body There are small necrotic areas which correspond to macroscopic pustules The absence of a horny layer in the oral mucosa produces the early erosions of the Koplik spots It is not for very long that anything has been known about the peculiar formation of giant cells with 50 to 100 nuclei which occur in the lymphatic tissue of the tonsils the respiratory tract and the esophagus and which have been seen in appendices removed during measles (Warthin and Finkelday after Ravina and Levy Lang³⁵⁶ Manigi and Minami after Rietschel³⁵⁷)

Among the anomalies of the exanthem must be named first its absence morbilli sine exanthemate Usually the Koplik spots too are absent in such cases³⁵⁸ of which a great number have been well corroborated by the presence of all other symptoms by the incubation period and by contact cases^{359 367}

While miliaria is common bullous measles are rare Confluent large bullae may though rarely cover and denude large areas so that the clinical picture of pemphigus results³⁶⁸ Hemorrhagic measles is rare this variety has been seen in combination with bullous measles³⁶⁹ Swelling of the upper lip of two to three days duration is in some epidemics so common that one author has spoken of a measles lip (Oxenius after Robert³⁶⁰)

Measles especially the hemorrhagic form is sometimes followed by gangrene of localized areas of the skin^{361 36} Related to these cases are the multiple ulcerations which are known as *ecthyma gangrenosum*³⁶³ which are occasionally seen after other infections too usually affecting infants Ecthyma gangrenosum starts on the buttocks with hemorrhagic necrotic nodules or larger foci of cellulitis and leads to deep punched out ulcers The mortality is high The condition is probably caused by secondary infection especially with pyogenic cocci and *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*)

³⁵⁵ Ravina A and Levy Lang E Histologic Diagnosis of Measles Specificity of Giant Cells Appendicitis Caused by Measles Ped 45 9 192 1937

³⁵⁶ Frasmann E Nachschon Exanthembildung bei Chwilt in Monatschr f Kinderh 27 510-511 1914

³⁵⁷ Koplik H Nachschon Exanthem Arch f Kinderh 84 190-193 1918
³⁵⁸ Ecthyma (bullous) Nachschon and Pemphigus bei Masern Monatschr f Kinderh 27 5 335 1914

³⁵⁹ Linehan J J Hemorrhagic Measles Brit M J 2 75 1914
³⁶⁰ Robert P Infectious Skin Diseases Other Than Tuberculosis and Leprosy Review of Literature of Dermatology 87 310-337 1913

³⁶¹ Thompson A Cases of Gangrene Following Measles Lancet 1201 754 1921
³⁶² Wistead J A Case of the Foot Following Measles J Pediat 6 34 193
³⁶³ Takahashi Ecthyma gangrenosum im Verlauf von Masern Arch f Dermat u Syph 120 732-780 1914

Measles may affect *pre existing skin diseases* in various ways. Infantile eczema³⁶⁴ and prurigo³⁶⁵ are often aggravated during measles³⁶⁶ either by internal causes or by scratching during the itching eruption and desquamation periods. Psoriasis seems to improve but returns during convalescence³⁶⁴. Measles like other acute infectious diseases often weakens the cutaneous tuberculin reaction. The predisposing influence to skin tuberculosis is recognized³⁶⁸. Disseminated exanthematic, apparently hematogenous cases of lupus vulgaris and tuberculosis cutis verrucosa are not very rare after measles in countries where skin tuberculosis is more prevalent than in the United States.

German Measles (Rubella)

The term German measles resulted from the long combined efforts of German clinicians of the nineteenth century to separate a mild measles like contagious disease from typical measles. When the International Medical Congress in London in 1881 tried to clarify the situation it was natural to speak of English measles and of German measles. Since then the entity has become widely recognized but there are still some dissenting unitarians. To prevent confusion it should be emphasized that the latin term rubiola is used for this disease in the German literature while in the English American terminology rubiola designates true measles (Dorland). The term rubella seems to be used only in the English speaking countries.

The cause of the disease is unknown. Children of 3 to 10 years of age are usually affected but no age group is immune. Lasting immunity after the disease is the rule.

The disease is best characterized by the often used expression mild measles. The prodromal symptoms of malaise, fever, coryza and sore throat which are not always present are much less pronounced than in measles. Children with German measles frequently come to the office of the dermatologist or are sent home from school because of the rash while a child with true measles is usually too sick to be ambulatory.

The incubation period of rubella is from two to three weeks. The fever is moderate and there is no photophobia or conjunctivitis. Excessive perspiration during the first to second prodromal days is a peculiar symptom (Stolte after Rietschel³⁶⁷). The palate and uvula are reddened and a few red follicles often appear along the midline (Forchheimer's sign) but there are no Koplik spots and the catarrhal symptoms if any are mild.

General lymphadenopathy is such an outstanding feature of the disease that Glanzmann advanced the theory that rubella is a disease of the lymphatic system not primarily an exanthem and therefore *toto caelo* different from measles.

³⁶⁴Beck C H. Immunity Against Psoriasis in Patient Who Have Previously Had Measles. *Ned r tidsskr v* (Copenhagen) 79: 4157-419, 1935.

³⁶⁵Costantino C. Sul comportamento dell'eczema di lattante durante il morbillo. *Clin. pediat* 12: 216-224, 1930.

³⁶⁶Volk R. Tuberkulose der Haut. *Hanb d H u C k* 10: 1, 1931.

³⁶⁷Rietschel H. Rubella. *Monatschr f Kinderh* 88: 312-35, 1941.

and scarlet fever. Almost all the peripheral lymphatic nodes are swollen and tender and the mastoid, occipital and posterior cervical glands, particularly of the left side, are so enlarged that the swelling often is not only palpable but visible. The lymphadenopathy starts before the exanthem and may outlast it by several weeks. This generalized lymphadenitis may be the only sign of rubella. In such exanthemless cases the diagnosis must depend on the accompanying circumstances, for example, contact cases with exanthem.²⁷⁰



Fig. 41.—German measles. Quite copious rash. (Courtesy Dr. Max Fox.)

The blood shows an initial leukopenia and a later eosinophilia (8 per cent). In the course of the disease the leukocytes rise and the increase of the plasma cells becomes marked, reaching 12 per cent.^{271, 2}

The prognosis is very favorable. The treatment is symptomatic.

Dermatomes.—The exanthem, which appears on the second or third day, follows in many ways the pattern of measles. It is usually seen first behind the ears and on the face but within one day it involves the whole body, occasionally large areas remain free. The fresh spots are rounder, more clearly defined and more regular than those of true measles. The most common size is that of a split pea, although the rash may consist of smaller or larger spots. The color is

²⁷⁰ Rietseh, I. H. Acute Infectious Exanthema. The Diseases of Children. By Pfau and Schlossmann. P. t. rman, vol. III. Philadelphia, 1935. J. B. Lippincott Company, pp. 213-233.

²⁷¹ Rietseh, I. H. Masern und Röteln. Monatsschrift für Kinderheilkunde 71: 54-60, 1917.

¹ Flöystrup, E. Rubella With and Without Rash. Brit. J. Child. Dis. 20: 20, 2, 19, 3.

² Moawitz, C. Röteln. Rubella. Handb. d. H. u. 24: 4, 7-429, 1910.

²⁷² P. rshack. Röteln. Thrap. d. C. g. nw. 63: 76-77, 1927.

red a shade less bright than in true measles and fades quickly. Often a confluent erythema develops on the face. The skin between the spots may, especially on the back, be diffusely red with the progress of the disease. Some epidemics have a pronounced hemorrhagic component³⁶³. The rash appears in successive crops each of which lasts about twenty-four hours. The whole exanthem lasts about three days. It fades in the order of the eruption³⁶⁹ occasionally with a light dusty desquamation and faint pigmentation³⁷². The face and neck may be cleared while the legs are still red.



Fig. 4.—German measles. Postauricular lymphatic nodes. (Courtesy H. Max Fox.)

The pharynx is diffusely red and the tongue often resembles the raspberry tongue of scarlet fever; that is, it is diffusely red, not coated, and the fungiform papillae are swollen.

Roseola Infantum (Exanthema Subitum)

John Zahorsky^{373,374} of St. Louis (in 1910 to 1913) separated from various little understood exanthematic diseases of childhood a typical entity to which he unfortunately gave the old name of roseola infantum. The term erythema

³⁷³Zahorsky J. Roseola Infantum. Survey of Literature. Arch. Pediat. 57: 405-409, 1940.

³⁷⁴Zahorsky J. Roseola Infantum in J. Brennenmann's Practice of Pediatrics, vol. II. Hagerstown, Md., 1937. W. F. Prior Company, Inc.

subitum³⁷⁵ has become more popular while Glanzmann's³¹⁸ unwieldy name critical three days fever exanthem of the infant is used only rarely.

The disease is an acute infection which at least in some countries attacks a large percentage of the infants. Roenbusch³⁷⁶ estimates that about 50 per cent of the young children become infected mostly at the end of the first year of life rarely after the third year.

The etiology is unknown but influenza has been suspected.³⁷⁷ The incubation period is seven days (from five to fifteen days Sobel³⁴⁴). Lasting immunity results from the infection but a few cases of repeated attacks have been observed.^{374, 378} About 40 per cent of the cases occur in summer and only 18 per cent in winter.³⁷⁹

The clinical picture is characterized by three days of continuous high fever and the eruption of a morbilliform rash immediately after the critical end of the fever. The onset is sudden sometimes alarming with convulsions,³⁸⁰ headache and vomiting. Sometimes however the children do not complain in spite of the fever. Complications are almost unknown and in many cases the general well being is not disturbed. Coryza and other mucosal symptoms and adenopathy are mild. There is a characteristic drop of the polymorphonuclear leukocytes (2 to 20 per cent) and a relative lymphocytosis and mononucleosis (80 to 98 per cent).³⁴⁸ These findings are most marked on the third day.³⁷³ The spleen is not enlarged. The prognosis is invariably favorable in spite of the sometimes alarming onset.

Dermadromes—The rash appears as Glanzmann³¹⁸ poetically puts it as the aurora of recovery after the fever period. It starts on the back and covers the trunk within twelve hours sometimes leaving the face the scalp and the extremities free. A second crop may then cover the limbs and remain visible when the first eruption has faded. The rash consists of slightly raised rose spots from 2 to 5 mm in size confluent or in irregular groups between which are small areas of normal skin. Later a large confluent erythema may appear on the back suggesting scarlet fever. There is no pruritus and the rash disappears in two or three days without pigmentation or desquamation. There is no characteristic enanthem an important differential feature.

The diagnosis may be difficult especially in isolated cases. The most important feature is the eruption at or after the fall of the temperature on the fourth day. In measles the rash appears at the height of the disease the whole syndrome is more severe and infections among siblings are common. In scarlet fever there is sore throat a typical tongue the exanthem appears early and

³⁷⁵ Veeder B S and Hempmann T C. Exanthema Subitum. JAMA 77 178 1789 1911

³⁷⁶ Roenbusch H. Exanthema subitum. Archiv f. Kinderheilk 69 1173 1175 1939

³⁷⁷ Opitz H. Masern Exanthema subitum. I. Arch. f. Kinderheilk 71 28 68 1939

³⁷⁸ Barabrig L H and Censpan L. Exanthema subitum. Am J Dis Child 68 943 993 1939

³⁷⁹ Bess B H J. Roseola infantum in New York State. J Med 41 1854 1859 1941

³⁸⁰ Crenthal R N. Roseola infantum. Wisconsin M J 40 55 7 1941

lasts much longer and there is desquamation and leukocytosis. Rubella which may look very much like roseola infantum has the characteristic lymphadenopathy. Erythema infectiosum rarely causes fever and the exanthem starts on the face especially over the bridge of the nose. Drug eruptions and toxic and infectious erythemas must be considered. No specific therapy is known.

Erythema Infectiosum

Erythema infectiosum which is also known under a number of other names for example fifth disease and megalerythema, is a moderately contagious infection of unknown cause usually affecting children. The disease occurs in epidemics of relatively small size often in institutions. The outbreaks are usually in late winter and spring. Animal inoculation and bacteriological studies have not been successful. However children have been infected by injection of blood taken at the height of the rash and by pharyngeal mucus.³⁴¹

The incubation period is about nine to fourteen days but it was only twenty-four hours in the experimental infections. There are no or very slight prodromes. The disease starts suddenly with a rash which is the main and sometimes the only symptom. The exanthem appears first on the face as small red spots which soon grow and coalesce forming an erythema which is most pronounced over the cheeks and which leaves the perioral and periorcular areas pale. The erythemas of the cheeks are often connected by a red isthmus over the base of the nose so that a butterfly figure results. The erythema is usually bright red³⁴² sometimes pink or cyanotic³⁴³ the fairly well defined edges are slightly palpable and raised and the surface is smooth and in every case hot to the touch. The chin is seldom affected the forehead is more often affected. The patient looks as if he has been slapped on both cheeks so definite is the erythema.³⁴⁴

One to two days later the erythema usually appears on the outer surfaces of the upper arms and sometimes on the buttocks and extensor aspects of the thighs.^{345 346} The lesions are slightly papular and have a tendency to grow peripherally and to fade in the center. Thus ring shaped garlandlike zigzag lattice³⁴⁵ honeycomb and other patterns result. The hands and feet are not affected. There is only slight fever no enanthem and little itching. From the third to the twelfth day the eruption fades but relapses may occur up to several months later. Atypical rashes affecting only the limbs are rare.^{346 347} Desquamation is usually lacking. In a small portion of the cases the face remains free.³⁴⁸ There

³⁴¹Taccone C. Sulla quinta malattia. Nuova epidemia osservata a Milano. *Pediatrica Arch. di pat. clin. pediat.* 3: 77-126 1918. *Jbl.* III 920.

³⁴²Chargin L. Scarlet fever and Cold in II. *Erythema Infectiosum Arch. Dermat. & Syph.* 47: 467-477 1943.

³⁴³Tobler L. *Erythema Infectiosum Ergebnisse inn. Med. u. Kinderh.* III 70-99 1915.

³⁴⁴Romeo Iorano A. *Erythema infectiosum Pediatría espan.* III 307-310 1934. *Jbl.* 51 55.

³⁴⁵Hissinger P. *Erythema infectiosum München m. d. Wechschr.* 1918. *Jl.* 1391.

³⁴⁶Lawton A. L. and Smith R. E. *Erythema infectiosum. Pp. 145-146 Arch. Int. Med.* 47: 28-41 1933.

³⁴⁷Rector J. M. *Erythema infectiosum—Clinical Observations J. Pediat.* 15: 540-545 1939.

■ moderate lymphocytosis and eosinophilia of 5 to 11 per cent^{369 370} (Zikowsky³⁶⁹ 20 per cent) during convalescence and later mononucleosis. Lymphadenopathy is uncertain. The children twice as many girls as boys³⁶⁷ are but little disturbed. Complications are hardly ever seen and fatalities have not occurred.

Febris Herpetica, Febris Ephemera, Febricula

Febris herpetica, febris ephemera and febricula comprise a group of fevers of unknown etiology characterized by ■ high temperature for about one day with the usual complaints of an acute febrile disease. In many of these short fevers *herpes labialis* appears, usually with sinking temperature or one or several days after the bout.³⁷⁰

Rubeola Scarlatinosa, or Fourth Disease, Dukes-Filatow Disease

Rubeola scarlatinosa is also called fourth disease and Dukes-Filatow disease. There is much objection³⁶⁸ to the acknowledgment as an entity of a febrile exanthem of which a few small epidemics have been observed.

After an incubation period of from nine to twenty days that is much longer than in scarlet fever the disease starts with a pink scarlatiniform slightly papular exanthem which covers the body within a few hours and does not always leave the circumoral area free. The face is generally less involved than the other parts. The rash fades after one to three days and is followed by a slight branny desquamation. The pharynx is red and the tongue only slightly coated.

The fever is mild and does not last longer than the rash. There are no important complications.³⁶⁸ There is no cross immunity with scarlet fever the mild cases of which the disease resembles.

Miliary Fever (Sweating Sickness)

About 200 epidemics of miliary fever or sweating sickness have been described since the first outbreak frightened London in 1486.³⁷¹ No sporadic or endemic cases have been observed. The epidemics usually occurred in spring or summer in an explosive form commonly restricted to relatively small areas like cities or valleys. The mortality of the epidemics varied from 0 to 90 per cent with an average of 8 per cent in the nineteenth century. This is a greater fluctuation than is known of any other epidemic disease. The horror caused by the high mortality of some of these epidemics was augmented by the sudden outbreak and the fulminating course. Frequently persons who had been in good health died within one or two days. More recently epidemics have occurred

³⁶⁹ Aeg. H. O. Blutkrankheiten und Blutdiagnostik ed. 5 Berlin 1921 Julius Springer

³⁷⁰ Zikowsky J. Erythema Infectiosum Wien klin. Wchnschr. 1933 II 843-847

³⁷¹ Hirsch C. F. b. i. h. sp. t. i. a. V. i. n. a. 190 Alfred Hirsch

³⁷² Hirsch A. Der Preis der h. i. t. o. l. e. s. c. h. und geographisch pathol. g. l. c. h. e. n. Standpunkt v. Chow. Arch. f. d. th. Anat. 8: 454-523 1855; 9: 176-171 1856

in France³²⁹ and Southern Germany and perhaps in Rumania³³¹. The first certain outbreak was observed in some French hamlets by L. Roussseau³³² in 1926 with hardly any variations from the classic picture. No epidemics have become known in America³³³. The cause of the infection is unknown. The incubation period^{333, 334} seldom exceeds one to two days but was found to be from ten to fifteen days in the cases of Stroc and Stroc³³⁵. Prodromes are either entirely lacking or consist of sudden weakness, malaise and muscular pains. The onset is abrupt, occurring frequently at night. A patient going to bed apparently in good health may awake with a chill, bathed in sweat and feeling dreadfully sick. Precordial oppression, a gripping dyspnea, nausea and muscular cramps together with premonitions of death constitute acute attacks which follow each other rather frequently and in increasing strength. At the height of such a paroxysm death may occur.

The spleen is enlarged. The urine secretion is small even to the degree of complete anuria. Delirium is common. The fever is usually high and remittent in type.

The convalescence is slow and relapses may occur. Immunity is not certain. Mild cases occur but adults are more severely affected than children. The pathological findings are unrevealing. The content of the vesicles is not sweat but a serous exudate. No specific therapy is known.

Dermadromes — The outstanding symptom after which the disease has been named is the excessive sweating (Timmermann³³⁴) which in contrast to sweats in other fevers starts with the rising temperature and continues throughout the duration of the fever. The sweating is so profuse that it is impossible to keep the patient even fairly dry by the most frequent changes of linen. The sweat is supposed to have a musty odor. After three to four days the characteristic rash appears. However many patients die before reaching the exanthematic second stage of the infection. The rash usually starts as a slightly papular eruption on the neck and chest and spreads in several crops over the whole body. The forehead and scalp are heavily affected and the face the least³³⁵.

The individual lesion is a red papule or macule with a central acuminate vesicle which is at first yellowish and clear but after one to two days is opaque. The exanthem may at times especially in children be quite morbilliform but confluent scarlatiniform and hemorrhagic varieties have been seen in some epidemics³³². The vesicles dry and crust after two to three days and heal with a branny or flaky desquamation. Oral lesions look like aphthae. The eruption is preceded by formication or tingling and accompanied by a feeling of relief.

³²⁹Roussseau L. La suette miliaire dans le Mont morillon. Bull Acad t med Paris 113 293 302 1935

³³⁰Stroc A. and Stroc H. Die kinderschweissfries krankh. Arch f kind ch 95 78 89 1931

³³¹Timmermann H. Der 'Schweissfrie' in Valais 1898 Alfred Hild

Onyala

Among the natives of West Central Africa occurs an acute febrile disease called onyala the main feature of which is a mucocutaneous eruption of hemorrhagic bullae. These lesions are usually found inside the cheek on the tongue and on the palate although bleeding may occur from all mucous membranes. There may also be localized hemorrhagic lesions of the skin. These blood blisters are umbilicated, trabeculated and filled with loosely coagulated blood. The disease may show all the features of a severe thrombocytopenic purpura.

Severe anemia, icterus, bronchopneumonia and central nervous system involvement are frequent. The mortality is high. There is profound thrombocytopenia with prolonged bleeding time, normal coagulation time, imperfect clot retraction and a positive tourniquet test. The intramuscular injection of whole blood is said to be a good method of treatment.³⁹⁵

Glandular Fever (Infectious Mononucleosis)

Glandular fever (E. Pfeiffer³⁹⁶) or infectious mononucleosis is a contagious febrile disease of unknown etiology characterized by generalized lymphadenopathy, splenomegaly and lymphocytosis. The incubation period is usually seven days. The terms glandular fever or prolonged fever³⁹⁷ of pharyngeal angina, thoracic abdominal nervous septic and other types characterize the great variability of the disease. The prognosis is good.^{398, 399}

Dermadromes—E. Pfeiffer³⁹⁶ emphasized the absence of exanthems and Glanzmann³⁹⁸ in his monograph on lymphemoid glandular fever elaborates on the lack of a characteristic rash. Other authors³⁹⁹ however have occasionally or frequently^{397, 400} seen erythema multiforme and lichenoid morbilliform diffuse erythematous maculopapular rose spot like or very rarely, purpuric exanthems. The rashes appeared during the first two weeks.

The epidemic in London in 1930 was marked by unusually frequent typhoid like rose spots which appeared before the lymphadenopathy. Recently a rash incidence of 14 per cent has been reported (Minkenhof after Robert⁴⁰¹). The blood count remains indispensable for the diagnosis. Of importance is the velvety red appearance of the gums which bleed easily. In severe cases the teeth may submerge in these fragile tissues. On other parts of the oral mucosa especially on the soft palate small grouped papules may appear and cause a granulated appearance. On such infiltrations shallow small or larger punched out, aphthous ulcerations may develop. Slight follicular and severe diphtheroid and

Black, W. I. Onyala. *B. Soc. Trop. Med. & Hyg.* 25: 707-26, 1931.

391 Pfeiffer, E. Das Drüsenfieber. *V. Sammlung d. utsch. Naturforscher und Arzt.* 7/11, 1895.

392 Tidy, H. L. Glandula Fever and Infectious Mononucleosis. *Lancet* 1934 II, 140, 236.

393 Glanzmann, F. Das lymphem. Drüsenfieber. *N. w. York* 1930, 8, Karger.

394 H. H. H. and Schwarz, F. Das Drüsenfieber. *Erz. b. d. Inn.* 33rd u. 34rd 62, 77.

395 1937.

396 W. J. J. Jr. TI. Lin. Friction and Fat. *Post. e. Wasmann* in *Infectious Mono-*

nucleosis (Glandula Fever). *Int. nat. Clin.* 2: 39, 1941.

ulcerative tonsillitis have often been reported.⁴ The oral ulcerations appear after the swelling of the submaxillary lymph nodes.

Unilateral *conjunctivitis* of a dry granular character is not rare.³⁹⁹ In exanthematic cases the Wassermann and Kahn reactions may temporarily become positive.⁴⁰⁰

Foot and Mouth Disease (Aphthous Fever)

Although the foot and mouth disease (aphthous fever) is predominantly an epidemic infection of cattle and other cloven hoofed animals it is occasionally transferred to man by contact with infected animals or drinking of their milk. The cause is a filtrable virus.

In man the infection has an incubation period of two days. The onset is sudden with fever, headache and malaise. On the following day salivation and an eruption of many umbilicated vesicles on the buccal and labial mucosa appear, the lesions being surrounded by a bright red areola. The tongue and the pharynx may be similarly involved. On the third or fourth day the disease enters a second stage.⁴⁰¹ New grayish or yellowish vesicles and larger blisters with or without red areolae may cover the hands and feet and even the legs.⁴⁰² The nail beds are often mentioned as the site of troublesome inflammations. The nails may be shed or they may show transverse grooves. Maculopapular, multiform and varicelliform exanthems involving the entire skin or much of it have been described.^{403, 404} The mouth condition together with diarrhoea, rhinitis and conjunctivitis and the symptoms of general infection may cause an alarming picture. Around the fifth day the symptoms subside and after ten days or more the patient is usually cured.⁴⁰⁵ The prognosis is good although some deaths have been reported. The treatment is symptomatic.

The identity of human and animal infection has been corroborated by successful inoculation of human material into cattle⁴⁰⁶ and guinea pigs.^{407, 408}

Dengue Fever

Dengue fever is an acute, nonfatal, widely distributed febrile disease of the warm climates. It is transmitted by various mosquitoes including *Aedes aegypti*, the carrier of yellow fever. The cause is a filtrable virus.⁴⁰⁹ The incubation period is about seven days.⁴¹⁰

⁴⁰ Von Schick J. Maul und Klauenuche beim Menschen. Klin. Wchnschr. 1: 630-63. 1931.
⁴⁰¹ Ariens L. 2 Fälle von Maul und Klauenuche beim Menschen. Berl. tärztl. Wchnschr. 37: 231. 1911.

⁴⁰² Gibbon A. H. A Case of Foot and Mouth Disease. Lancet: 19: 41. 1933.
⁴⁰³ Tappin R. G. Maul und Klauenuche beim Menschen. Arch. f. Dermat. u. Syph. 180: 189. 201. 1940.

⁴⁰⁴ Cerlach. Maul und Klauenuche beim Menschen und Übertragung auf Meerschweinchen. Wchnschr. 37: 210. 1914.

⁴⁰⁵ Bertarelli. Übertragung der Maul und Klauenuche auf den Menschen und Wiederimpfung der menschlichen Krankheit auf die Rinder. Zbl. f. Bakteriol. 45: 9. 1907.

⁴⁰⁶ Waldmann O. and Pape J. Experimentelle Untersuchung über Maul und Klauenuche. Berl. tärztl. Wchnschr. 37: 349-354. 1911.

⁴⁰⁷ Uhlir H. H. Übertragung der Maul und Klauenuche auf Meerschweinchen. Dtsch. med. Wchnschr. 47: 671-672. 1921.

⁴⁰⁸ Simmons T. S. Dengue. M. Clin. North America 27: 809-81. 1913.
⁴⁰⁹ Kilner P. and Lisansky E. T. Dengue. Ann. Int. Med. 20: 41-51. 1914.

The disease starts with severe frontal headache and pain in the lower back in joints and in muscles. Chills are marked and indolent lymphatic nodes are palpable over the posterior scalenus muscles.⁴¹¹ There is bradycardia in spite of the high fever, and leukopenia with a shift to the left. The temperature falls to normal on the third day but fever often returns after one to two days (saddle back curve). The second fever is sometimes higher and ends by crisis around the seventh day. Deaths are very rare but convalescence may drag out over several weeks. No specific laboratory test nor treatment has been developed.

Dermadromes—The initial fever is often (38 per cent, Simmons⁴⁰⁹) accompanied by an erythematous symmetric rash or extensive flushing which is most pronounced on the face, neck, chest, forearms and palms.⁴¹² The eyes are reddened also. This flushing is out of proportion to the temperature and was seen in about 26 per cent of the cases during a recent major epidemic.⁴¹⁰ The flushing subsides gradually. If there was any erythema of the chest it may be converted into the secondary rash which does not involve the face. This secondary or terminal exanthem was seen more often (37 per cent, Kissner and Lisansky⁴¹⁰, 86 per cent, Simmons⁴⁰⁹). It appears between the second and sixth days and is macular occasionally maculopapular, carlatiniform or rarely hemorrhagic. It usually starts on the chest, back or abdomen and spreads to the trunk but this sequence may be reversed if the rash starts later in the illness. No definite relationship seems to exist between the onset of the second fever attack and the terminal rash which is followed by an imperfect desquamation and itching of the palms and soles.⁴⁰⁹

Some authors emphasize the sweating and the variability of the rashes.⁴¹³ Complicating pyodermatoses are common.⁴¹⁴

Pretibial fever—An epidemic febrile illness of approximately five days duration characterized by slight respiratory symptoms, headache, leukopenia, palpable spleen and a symmetrical maculopapular rash mainly over both pretibial areas vaguely resembling erythema nodosum has been observed among troops in South Carolina.⁴¹⁵ The rash was present in 80 per cent of the forty cases. All efforts to determine the nature of this pretibial fever were in vain.

Phlebotomus Fever

Phlebotomus papatasi or sandfly fever is a benign sandfly borne virus infection of hot and dry countries characterized by a fever of two to four days duration, severe frontal headache and eye ache, photophobia and muscular pains. There is leukopenia and shift to the left. The face is described as "curi-

⁴¹¹ Stewart H. H. Dengue U. S. Nav. M. Bull. 42: 1233-1476, 1944.

⁴¹² Angstein L. Yellow Fever and Dengue J. Pediat. 22: 612-617, 1943.

⁴¹³ Misalzu H. Beobachtung n. b. l. einer Epidemie von Dengue Fieber mit mannigfaltigen Symptomen Acta dermat. 20: 85-86, 193. Zbl. 45: 1.

⁴¹⁴ Dracoulides N. Observations dermatologiques sur les cas de la dengue (pendant la pandémie d'Athènes en 1941) M. Bull. Soc. franç. dermat. et syph. 36: 612-615, 1949.

⁴¹⁵ Daniels W. B. and Crumman H. A. Pretibial Fever an Obscure Disease J. A. M. A. 122: 361, 1943.

ously red and puffy in contrast to the body ^{416 417} and may stay so for weeks after the fever. The conjunctivae are red and there is photophobia. Crops of vesicles at the junction of the hard and soft palates⁴¹⁸ (not seen by other observers) and probably only in a minority of the cases purpuric scarlatiniform morbilliform urticarial and erythema multiforme like evanescent rashes⁴¹⁷ and perifollicular erythema in the axillae and about the elbows and knees have been mentioned. Herpes is not a feature ^{418 419} but occurs occasionally⁴¹⁷ in severe and atypical fashion.

Bullous reactions and severe edema following sandfly bites after convalescence are interpreted as allergic reactions ⁴¹⁷

⁴¹⁶Walker A S and Dods L. Epidemic of Sandfly Fever in Palestine During 1940. *N J Australia* 33 345-349 1941

⁴¹⁷Marchionini A. Haut- und Schleimhautschinungen II im Pappatacifeber in Anatolien. *Arch f Dermat u Syph* 182 613-651 1942

⁴¹⁸Schilling C. Pappatacifeber. *Handbuch der inneren Medi* in vol I Berlin 195 Julius Springer

⁴¹⁹Sabin A B Philip C B and Paul J R. Phlebotomu (Pappatacior Sandfly) Fever. *J A M A* 125 693-700 1944

CHAPTER V

SYSTEMIC INFECTIONS

Varicella (Chicken Pox)

In 1931 Tezner⁴⁰ in a comprehensive review of the subject stated that the causative agent of varicella (chicken pox) has often been searched for and almost as often found. This is a witty overstatement. We know that it is a dermatropic probably filtrable virus related to but not identical with Pfschen's elementary bodies which cause variola and vaccinia. Injection of the content of the vesicular lesions of chicken pox into the rabbit's cornea produces within twenty four hours a small vesicle which bursts after seventy two hours. The microscopic picture of the cornea is quite characteristic, especially the giant cells with large eosinophile inclusions found by Gins (see Tezner⁴⁰). Tyzzer (after Lipschutz⁴¹) found nuclear inclusions which Lipschutz⁴¹ believed to be microscopically identical with the inclusions found in herpes zoster (zoster bodies).

The virus is contained in the skin lesions and probably in the blood stream. Experimental skin infection with nasal mucus has been as unsuccessful as the infection of the tonsils with vesicular fluid but the intradermal inoculation of blister serum produce after nine days a typical vesicle which always remains localized and can be successfully used for further inoculations. The inoculation is unsuccessful in persons who have had varicella. It immunizes against chicken pox with considerable reliability⁴².

Droplet infection through the lungs seems to be the most important way of contagion. Indirect transfer is negligible.

Chicken pox is endemic and epidemic usually affecting children. Varicella has a good prognosis unless one of the rare complications occurs. Newborn infants and adults are much less frequently but usually more severely affected⁴³. The infection is followed by long lasting immunity.

The incubation period varies from seven to twenty six days but is usually thirteen to fourteen days. Prodromes are little marked. Fever is common, especially in older children or adults and convulsions, sleepiness, photophobia and gastrointestinal symptoms may occur. Very short lived prodromal or initial rashes are not common (1 per cent). They are mostly scarlatiniform rarely

⁴⁰Tezner O. Varicell n Ergebn d inn Med u I ind rh 41 303 6 2 1931

⁴¹Lipchutz B. Di Ein chluskrankh it n d r Haut Handb d It u Ck II 1 164 1930

⁴²Lipchutz B and I und atitz K. Ueber die Aetiologie des Zoster und Ueber s ine Bezi hungen zu Varicell n Wien klin Wchn chr 38 499 03 19 5

⁴³Greenhalgh M. Prophylaxis of Varicella With Vesicle Fluid. Am J Dis Child 31 851 855 19 6

⁴⁴Warrig J J. Nuburger K. and G v r E F. Chickpox 9 v r Form in Adult Arch Int Med 69 394-400 1940

⁴⁵Nebe Karl. Ueber Varicella bei Erwachsenen. Leipzig 1931 Dissertation

morbilliform or polymorphic and seem to forecast a more severe course. Giant cell formation in the tonsils similar to that seen in measles has been found in chicken pox during the prodromal stage.⁴⁴ All symptoms may be absent and the exanthem may break out with the patient in apparently good health. This conspicuous lack of sick feeling often causes the child with varicella to be brought to the office of the dermatologist because the idea of a systemic infection does not enter the mother's mind. This rarely happens in the other important exanthematic diseases of children.



Fig. 43.—Varicella. (Courtesy Dr. Max Fox.)

Dermadromes—The eruption starts on the face and on the scalp, that on the body (back) being only slightly later, though some isolated vesicles may precede the main eruption. The distribution of the exanthem, which may develop fully in one to two days, is most dense on the trunk and becomes lighter toward the extremities and the acra. This centripetal tendency is in marked contrast to the centrifugal distribution of the variola pustules, which leave the trunk and especially the abdomen relatively free and crowd on the hands and feet. The individual lesion appears as a small macule which in twenty-four hours develops into a clear vesicle which is often surrounded by a relatively wide bright red areola. The blister is sometimes oblong, rarely pustular or hemorrhagic. Pri-

⁴⁴Tomlinson, T. H. Chicken pox. Giant Cell Formed in Prodromal Stage. *Am. J. Path.* 15: 53-526, 1939.

may umbilicate of the filled lesions is rare though early rupture depression and formation of a sunken crust in the center may suggest umbilication but should not be taken as such. The vesicle is multilocular, but the septa as well as the wall are much thinner than in small pox so that the lesion often can be wiped off with a rough towel. The blister is quickly followed by a crust which



Fig. 44.—Bullous and hemorrhagic lesions of varicella. (Courtesy of Division of Dermatology, Department of Medicine, University of Chicago.)

may adhere for many days or as long as two weeks. A few larger and deeper lesions may leave pitted scars with pigmented margins but the marks are rarely disfiguring. The lesions are more numerous on irritated or macerated skin. The exanthems vary in density from a few lesions to a copious eruption of many hundreds of efflorescences in all stages of development. This latter peculiarity is due to the appearance of successive crops and to the fact that the individual lesion may become arrested in any stage of development. The crops may be

accompanied by mild fever. After one week the crops stop appearing although miliaria like weak eruptions may continue to follow. The last eruptions are mild and the lesions usually fail to mature to vesicles.

There are several *clinical varieties* of chicken pox and its complications^{4, 5, 6, 7}. The eruption may form bullous, impetiginous or crulescent lesions. Confluence indicates a severe infection.



Fig. 45—*Varicella gangrenosa*. Fatal case. (Courtesy Dr. Max Fox.)

Varicella pemphigoides is a rare variety characterized by large flaccid bullae with adherent centers. Such cases may be accompanied by high spiking temperatures³³ and have repeatedly taken a fatal course^{4, 6}. Some of these cases seem to be a combination of varicella and secondary pyogenic infection. Erysipelas is a dangerous complication. In some cases the vesicles remain very small; this is called *miliaria varicellosa*.

In *varicella gangrenosa* the normally fast sequence of drying and crusting of the vesicles is disturbed by a progressive necrosis which leads to punched out gangrenous ulcers. The floor of these ulcers is covered with necrotic greenish material. Hemorrhagic features are common so that the ulcers often appear black. However, an occasional black discoloration of the otherwise normal crusts does not warrant the diagnosis of gangrenous chicken pox. Several ulcers may coalesce so that palm sized gangrenous defects ensue which may even lay bare the underlying muscles. In some instances the gangrene started in apparently normal skin and not from the vesicles.

³³ Ronald, M. C. W. and H. H. R. W. H. Chicken pox: Anomalous Form. Brit. J. Child Dis. 33: 36, 1929.

³⁴ Schwartzman, J. Varicella and Impetigo Acute. Arch. Pediat. 67: 9, 1910.

Gangrenous varicella is a severe disease with high temperature prostration and often fatal course. Infants and sick young ters are more likely to develop this complication than older and otherwise healthy children. Scarlet fever diphtheria and tuberculosis are among the predisposing diseases. Banks and McCartney,⁴¹ in a fulminating case of massive skin gangrene in the eruptive stage of varicella found streptococci to be the causative organism. Hemolytic streptococci are also the cause of dangerous cellulitis and of erysipelas and lymphadenitis. Infected lymph nodes usually break down and form abscesses. Cutaneous complications amount to 57 per cent of all the complications of chicken pox⁴². The incidence of gangrenous varicella amounts to about 1 per cent⁴³ but seems to be much smaller in the United States. More than one half of the reported cases of gangrenous varicella ended fatally.



Fig 46—Hemorrhagic and unusually copious varicella. (Courtesy Dr. Max Fox.)

Knoepfelmacher⁴⁴ separates from other purpuric manifestations in varicella the prodromal purpura and the purpura which occurs not too infrequently in mixed infection of pertussis and varicella. The varicella eruption is rarely hemorrhagic from the start. The vesicle content may become bloody or there may be other purpuric features. The whole syndrome of thrombocytopenic purpura⁴⁵ may develop during or after the infection in rare instances together

⁴¹Banks H. S. and McCartney J. E. Varicella (angr. nosa) Due to Streptococcus pyogenes. Lancet 1937 II 311-314.

⁴²Bullowa J. M. and Wihlik S. M. Complication of Varicella That Occurs Among 234 Patients. Am. J. Dis. Child. 49: 939-969 1937.

⁴³Knoepfelmacher. Varicellen und Hautblutungen. Wien. med. Wochenschr. 1916 p. 990.

⁴⁴Cohen H. J. Acute Thrombocytopenic Purpura Following Varicella. Arch. Pediat. 52: 377-1936.

with massive skin gangrene⁴³ Progenic sepsis has been blamed in some of these cases⁴⁴

The diagnosis of chicken pox is only difficult in unusual types in isolated cases or in times of a smallpox epidemic. Many authors discuss the differential diagnosis of chicken pox and smallpox⁴⁵⁻⁴⁸ (Tieche after Tezner⁴⁹). The most important points are: In chicken pox as compared with smallpox the prodromes especially fever are mild or lacking. The distribution of the rash is centripetal starting and massed on the trunk. It appears in crops and the lesions show different stages of maturity. The lesion is generally less round and less firm so that it can be wiped off and it is rarely umbilicated. The halo (corona) is more irregular wider and it develops faster. These criteria should all be taken with a grain of salt and the diagnosis should not rest on any one sign or symptom. (See also under Variola)

No specific laboratory test for chicken pox has come into general use so that a negative Paul's test for smallpox may in certain cases become an important diagnostic aid.

Occasionally *Kaposi's varicelliform eruption* a rare acute vesiculopustular eruption with severe systemic reactions may have to be considered. In most of the known cases the rash was superimposed on atopic dermatitis. The umbilicated lesions resemble vaccinia more than varicella but they appear in crops and the Paul test is negative. There is increasing evidence that the disease is a generalized herpes infection⁴²⁻⁴³.

Herpes Zoster and Varicella

As far back as 1891 Von Bokay⁴⁶ published reports of five different instances of chicken pox in children following herpes zoster in a parent or other contact after a period approximately equal to the incubation period of varicella. These observations apparently easy to check were almost ignored until in 1909 the same author⁴⁶ presented a second series. Since then far more than 300 cases have become known and the puzzling matter continues to appear in additional publications⁴¹. The most common type of relationship between the two diseases is an outbreak of varicella in one or several persons who have had con-

⁴³Grosser A. J. and Lockwood W. W. Varicella Complicated With Thrombocytopenic Purpura and Gangren. J. Pediat. 12: 641-647 1939.

⁴⁴Wesselschott G. Differential Diagnosis of Chicken pox and Smallpox. New England J. Med. 230: 15-19 1944.

⁴⁵Ladlow P. W. Smallpox and Chickenpox. Differential Diagnosis. New York State J. Med. 38: 310-312 1939.

⁴⁶Blattner R. J. Heys F. M. and Harrison M. L. I. Etiology of Kaposi's Varicelliform Eruption. J. Pediat. 27: 707-715 1945.

II Lynch F. C. Kaposi's Varicelliform Eruption. Arch. Dermat. & Syph. 51: 19-137 1945.

⁴⁷Lane G. W. and Herold W. C. Kaposi's Varicelliform Eruption. Arch. Dermat. & Syph. 50: 396-404 1944.

⁴⁸Evans C. H. Bollin A. S. and Steves R. J. Kaposi's Varicelliform Eruption. Arch. Dermat. & Syph. 51: 134-135 1945.

⁴⁹Von Bokay J. Ueber den aetiologischen Zusammenhang der Variellen mit gewissen Fällen von Herpes Zoster. Wien klin. Wchnschr. 1909 p. 1773. J. b. b. f. Kinkle b. 103: 8-13 1914.

⁴¹Blatt M. I. Zeldes M. and G. in A. F. Chickenpox Following Contact With Herpes Zoster. Minor epidemics. J. Lab. & Clin. Med. 25: 951-955 1940.

⁴²Baker L. F. Circallid Herpes Zoster in Cases. Arch. Dermat. & Syph. 40: 974-976 1939.

tact with a person suffering from herpes zoster. In several instances accidental chicken pox infection from other sources could be fairly conclusively ruled out for example in Lynch's⁴³ case by the fact that the hospital where the case occurred was in quarantine for twenty one days because of scarlet fever while the incubation period of chicken pox rarely exceeds seventeen days. Occasionally



Fig. 47.—Herpes zoster in varicella. (Courtesy of Division of Dermatology, Department of Medicine, University of Chicago.)

secondary cases of varicella developed from those varicella cases which stemmed from herpes zoster, thus proving their true chicken pox nature. However, these infections did not prove as highly contagious as is usual.^{43, 44} The appearance of herpes zoster after contact with chicken pox is seven times rarer than chicken

⁴³Lynch F. W. Herpes Zoster and Chickenpox. *Arch. Internat. Med.* 44: 68-69, 1911.

⁴⁴Monticelli M. Herpes Zoster-varicella. *Bull. Soc. Ital. Pediat.* 3: 183, 189, 1931.

pox after zoster⁴⁰ Very rare too are the sequences chicken pox—herpes zoster—chicken pox or zoster—zoster—chicken pox or other alternations Chicken pox simultaneously with or following herpes zoster in the same person usually an elderly man, varicella with herpetiform groups of vesicles and herpes zoster with aberrant or generalized lesions have been reported⁴¹⁵ The cases in which



Fig 48—Varicella in adult with herpes zoster Same patient as in Fig. 47 (Courtesy of Division of Dermatology Department of Medicine University of Chicago)

one disease followed the other have been interpreted in favor of a close relationship or identity of the diseases⁴¹⁶ as well as to prove their different nature since immunity which probably follows herpes zoster and certainly follows varicella would be more likely to prevent the sequence than to produce it⁴¹⁷ The interpretation of the relationship between herpes zoster and varicella as a fortuitous one is refuted by the apparent lack of any co occurrence between for example herpes zoster and measles which should occur just as often if coincidence were the only factor The most interesting experimental study was made by K

⁴⁰Fleming J Herp and Varicella Simultaneously in Same Patient Glasgow M J 122 7 73 1939

⁴¹Ferriman B C Chickenpox and Herpes Zoster in Same Patient Lancet 1939 I 930-931

⁴¹⁵Schönfeld W Herpes Zoster und Herpes Simplex Handb d H u Chk 7 1 112 19 9

Kundratitz⁴⁴⁸ who in seventeen out of twenty eight cases successfully inoculated herpes zoster into children who had not had chicken pox. Two of the inoculated children developed after the varicella incubation period a generalized eruption identical with varicella. The inoculation was never successful in children who had had chicken pox and those children who had been successfully inoculated with herpes zoster or who had been treated with zoster convalescent serum proved to be immune to varicella. Lipschutz⁴⁴⁴ found nuclear inclusion bodies



Fig 49.—Chickenpox and herpes zoster. The chickenpox preceded the eruption by a few days (From Topf and H. Handbook of Communicable Diseases The C. V. Mosby Company)

which he believed to be characteristic of both diseases in the inoculation reactions of Kundratitz's⁴⁴⁸ cases. Kundratitz's experiments were on the whole confirmed by Bruusgaard⁴⁴⁹. Experimental infection with varicella stemming from herpes zoster just by placing the beds of the children close together was accomplished several times by Brulinsky⁴⁵⁰. A new contribution is the finding of similar inflammatory changes in the spinal ganglia in varicella as are known to occur in

⁴⁴⁸ Kundratitz H. Experimentelle Übertragung von Herpes Zoster auf den Menschen und die Beziehung von Herpes Zoster zu Varicellen. Monatschr f. Kinderh. 29: 516 '93 19.5.

⁴⁴⁹ Bruusgaard E. The Mutual Relation Between Zoster and Varicella. Brit. J. Dermat. 44: 124 193.

⁴⁵⁰ Brulinsky F. Herpes Zoster und Varicella. Kiev med. Zh. Nr. 3 and 4 43: 53 1930 Zbl. 35: 351.

herpes zoster⁴³¹ Some authors believe that the incidence curve of herpes zoster and varicella runs parallel

All theoretical explanations of the relationship between herpes zoster and varicella have so far remained unsatisfactory⁴³²⁻⁴³⁵ mainly because of varicella zoster cases in the same person Unitarian and dualistic schools of thought have formed ranging from complete denial of any relation to close relationship with dermatotropism of the virus in varicella and neurotropism in zoster The matter is still highly controversial⁴³⁶ however some relationship cannot be doubted

Vaccinia

Vaccinia is an infection of cattle caused by a virus which seems to be identical with that of variola Animal passage probably has modified the infection in many respects It almost always causes a characteristic pustule at the site of infection followed only in extremely rare instances by generalized eruptions

The disease leaves the patient immune to vaccinia and smallpox Spontaneous infections with vaccinia are quite rare and occur mostly in dairy personnel The intentionally produced infection with vaccinia however is one of the most common and widely studied infectious diseases of the civilized world Though produced in order to attain a systemic effect that is immunity against variola vaccinia is usually not thought of as a systemic infection

The first three to four days after inoculation is the symptomless incubation period On the fourth day a raised papule (papilla) with a narrow red halo (aurea) appears On the sixth or seventh day the papule changes into an umbilicated vesicle surrounded by a wide areola Between the eighth and tenth days the infection is at its height and often accompanied by lymphadenopathy fever and leukocytosis According to some authors the spleen is palpable for a short while The involution of the pustules starts on the eleventh day Three to four weeks after the vaccination the local process has wound up with a scar

The apparently solid papule appears histologically to be a vesicle with many chambers There are characteristic vacuolizations of the cytoplasm characterized by Unna⁴³⁷ as balloonizing and reticular degenerations The first term was chosen because of the vacuolization which finally leaves the prickly cells looking like bags filled with balls the nuclei The epithelial and other cells of the vesicles contain the variola vaccinia virus Inoculation of the vesicle content into the cornea of the rabbit (Prid's test) produces in thirty six hours characteristic epithelial papules with central crateriform necrosis The microscopic examination demonstrates many Guarnieri bodies⁴³⁸ Paschen's elementary bodies can be demonstrated in smears from early lesions by staining They resemble cocci but they are smaller

⁴³¹Balogh E V Zur Pathogenese des Windpockenreizes (Ein Beitrag zur Frage Varicellen und Nervensystem) V H Z Internat Long III 2 232 241 1936

⁴³²Nohara F J Beobachtung von Zoster gleichzeitig mit Varicellenausbruch bei dem oben Kranken Dermatologica 79 29-43 1939

⁴³³Bassau C Kummer I Nagel O Rill J H und Schenfeld W Mitteilung zwischen Zoster und Varicellen Dermat Wochenschr 193 I 209 214

⁴³⁴Pasch H F Vaccine und Vaccinenausbruch Handb d H u Ck 2 161 297 193

A great number of investigations have shown that the vaccinia virus enters the blood stream and appears in the air passages in almost all the organs⁴⁵⁵ and in the secretions for example the urine⁴⁵⁶

The blood of vaccinated children without any complications may, from the third to the tenth day produce typical vaccinia in nonvaccinated children (H and K Herzberg after Paschen)⁴⁴

Dermadromes—In spite of the generalization of the virus which probably occurs in all cases hematogenous skin infection and development of typical lesions are extremely rare. These lesions must be separated from accidentally inoculated vaccinia on eczematous skin on the lips on the eyes or on other susceptible parts



Fig. 50—Vaccinal rash. (Courtesy Dr. Max Fox.)

of the surface (eczema vaccinatum). True *generalized vaccinia* appears possibly after the third day but usually during the second week after the vaccination as a popular rash which passes through vesicular and pustular phases though not with the precision of the inoculated vaccinia. The eruption is disseminated sometimes universal. Exanthems are known. Sometimes the neighborhood of the original vaccination for example the same arm is especially involved. The content of the pustules produces characteristic lesions in the rabbit cornea and in the skin of nonvaccinated persons. The eruption is accompanied by moderate

⁴⁵⁵Cins H A Hackenthal H and Lame tz wa Natali Neu Erfahrung n und V rsuch über di Generalisierung d s Vak in virus Centralbl f Bakteriol 110 115-119 10 9 Experimentell Untersuchung n über di Centralbl f Bakteriol 110 4 9-441 10 9

⁴⁵⁶Wohlitz U ber Vaccinagen rali sta u d Nachwei des Virus im Urin Zbl 57 457-458

fever and splenomegaly. The differentiation from variola and varicella may be of practical consequence. In contrast to smallpox there are no severe prodromes and no initial rash. There is no drop in temperature following the eruption. The acme is reached at the time of pustulation and is followed by slow lysis. The pustules have no areola; they are larger and they heal without scars (Drago after Paschen⁴⁵⁴). Severe varioliform cases with fatal outcome have been described.⁴⁵⁷⁻⁴⁵⁸⁻⁴⁵⁹ The microscopic picture in Shortt's⁴⁵⁵ case was that of



Fig. 51.—Hemorrhagic and extremely generalized varicella. (Courtesy Dr. M. A. Fox.)

vaccinia. Corresponding changes were found in focal lesions of the spleen and liver.⁴⁶⁰ A pemphigoid eruption of the fetus after vaccination of the mother may occur.⁴⁶¹

Morbilliform urticarial bullous or rarely erythema multiforme like exanthems occasionally appear during the second week, rarely earlier.

⁴⁵⁷Anders. Allg. Kuhpocken mit tödlich Ausgang. Ztschr. f. Hyg. u. Infektionskr. 116, 1919.

⁴⁵⁸Shortt G. T. de V. r. Ca. of Generalized Vaccinia. Lancet 1933 I, 9-11.

⁴⁵⁹Mekhann C. F. and Ross H. A. Generalized Vaccinia and Poxema Vaccinatum. M. Clin. North America 2, 785, 1938.

⁴⁶⁰Ross R. A. Virus and Rickettsial Diseases. Cambridge, Mass., 1940. Harvard University Press.

⁴⁶¹Lynch E. W. Dermatologic Conditions of the Fetus. With Particular Reference to Variola and Vaccinia. Arch. Dermat. & Syph. 28, 997, 1919, 1932.

These eruptions may be analogous to the initial rashes in variola. The postvaccinal rashes have rarely been seen after revaccination⁴⁶. The cause of postvaccinal rashes as well as of true generalized vaccinia is thought to be a disturbance of the antibody formation. Normally these substances are produced in sufficient quantities to neutralize the virus in the blood stream so that no exanthem appears. In other cases enough of the blood borne virus reaches the skin to cause an erythema. In the papulovesicular generalized vaccinia, the antibodies are so weak or they appear so late that the virus deposited in the skin can complete a fairly normal development (Czerny and Opitz after Groth^{463 464}).

Hemorrhagic vaccinia and *purpura* after vaccination are very rare^{465 466 467} (Voigt after Paschen⁴⁶⁴). The pustules are black and they bleed; there are signs and symptoms of thrombopenic purpura. The prognosis seems favorable.

Some authors claim that the number and quality of the scars of the first vaccination indicate the degree of immunity which has been reached (Gregory after Paschen⁴⁶⁴)⁴⁶⁸. In spite of great numbers of observations in revaccinated children no consensus has been reached. Armstrong⁴⁶⁹ found that out of seventy-one cases of postvaccination encephalitis in America seventy followed vaccination with one scratch only. It is conceivable that too little skin reaction may not produce sufficient immunity to protect against such complications.

Psoriasis may either develop at the site of the pustules or increased psoriatic activity and spreading may follow. While the localized eruption can be interpreted as a Koebner phenomenon (provocation of psoriasis by local irritation) the flare up and generalization of psoriasis is well known to occur after many infections.

The relation of so called *milkers' nodules* on the hands of dairy personnel to true vaccinia is controversial^{464 470 471}. Vaccination does not seem to immunize against milkers' nodules (Nagel after Robert³⁶⁰). Rashes similar to postvaccinal eruptions have been observed⁴⁶ in milkers' nodules.

⁴⁶³Reffs G. Polymorphes Exanthem als Komplikation einer akzidentellen Vakzination. *Dermat. Ztsch.* 60: 200 1915 1931.

⁴⁶⁴Groth A. Vaccinagenrelata. *Zbl. f. d. ges. Hyg.* 16: 865-867 1929.

⁴⁶⁵Groth A. Zur Ätiologie der Milkenknoten in München. *med. Wchnschr.* 78: 2128-2130 1929.

⁴⁶⁶Paschen H. Fall von Purpura im Anschluß an die Impfung. *München. med. Wchnschr.* 1907 p. 1801.

⁴⁶⁷Houston T. C. Purpura Associated With Vaccination. *Canad. M. A. J.* 43: 593-594 1940.

⁴⁶⁸Schwartz A. H. Postvaccinal Purpura. *Case. Am. J. Dis. Child.* 30: 856-858 1925.

⁴⁶⁹Kandler H. Die Impfung als Indikator der Immunität gegen Variola und Vakzine. *Veröffentl. d. Geb. d. Med. V. walt.* 42: 363-404 1934.

⁴⁷⁰Armstrong Charles. Postvaccination Encephalitis. With Special Reference to Prevention. *Pub. Health Rep.* 47: 1553-1565 1932.

⁴⁷¹Oppenheim M. and Feistner A. Leber Milkenknoten. *Arch. f. Dermat. u. Syph.* 159: 334-342 1930.

⁴Schultze W. and Crundhoffer F. J. Ueber Milkenknoten mit toxischem Exanthem. *Arch. f. Dermat. u. Syph.* 158: 115 1929.

⁵Olguin A. and Morozov M. I. Histology of Milkers' Nodes. *Soviet. Dermat. u. Ven. f. Dermat.* 9: 338-353 1931. *Zbl.* 39: 289.

⁶Stark A. M. and others. Über die Pockenätiologie der sog. Milkenknoten. *Arch. f. Dermat. u. Syph.* 170: 35-60 1934.

⁷Worring F. Deux nouveaux cas de tubercules du trayeur. *Bull. Soc. franç. d. dermat. et syph.* 41: 19-203 1934.

⁸Pommes H. J. Leber Milkenknoten. *Dermat. Wchnschr.* 98: 134-14 1934.

⁹Kren H. Milkenknoten mit Exanthem. *Wien. klin. Wchnschr.* 2: 1581 1930.

Variola (Smallpox)

Smallpox is an extremely contagious usually epidemic disease. It is caused by a virus in many points identical with that of vaccinia^{454 477}. As in vaccinia the agent is contained in the cellular inclusions found in the lesions (see vaccinia). The characteristic inclusions Guarnieri's bodies can be demonstrated in the small grayish ulcerated papule which develops after inoculation into the rabbit's cornea (Paul's test). The disease is probably contagious even in the initial stages. The virus is spread by contact droplets dust or contaminated persons and objects. The crusts of the healing lesions are highly contagious as are the bodies of persons who have died from the disease. Air and sunshine destroys the germs which otherwise are able to survive for a long time. The disease confers immunity although occasional reinfections have been reported. Almost all persons who neither have had smallpox nor have been vaccinated during the preceding ten years are susceptible. The fetus may become infected and be born with an exanthem or with scars.

The incubation period is twelve days with some variations and it is a rule that the shorter the incubation the severer the course. Thus in hemorrhagic smallpox the incubation period is often only eight days while in the mild variola minor the incubation period may be twenty one days⁴⁵⁴. The onset of the disease is abrupt. The patient is severely ill with high temperature frontal headache and intense lumbar and other muscular pain. Vomiting and constipation may be present. Delirium is common. The skin is flushed and hot. Women often start to menstruate at the outbreak of variola sometimes before the expected day. Most authors agree that severe prodromes do not necessarily usher in a severe eruption although a mild initial stage is usually followed by a mild course.

Dermatomes.—A peculiarity of the prodromal phase of variola is the initial rash which is observed in 15-30 per cent of the cases. It most often develops on the second day and is morbilliform or scarlatiniform rarely urticarial. The morbilliform rash starts on the face and travels within a few hours over the body and especially over the extremities. It is most often recognizable on the sides of the body on the extensor surfaces of the extremities⁴⁵⁸ and on the mammae. It vanishes as quickly as it appears. Some authors⁴⁷⁸ believe that the purely macular non petechial rash is of favorable prognostic significance but this is not always true⁴⁷⁸. More importance is given to the much rarer scarlatiniform rash. In this variety which may be seen on the very first day of the prodromes the abdomen below the navel and the inner thighs are flaming red. Within this somewhat triangular shaped area (Simon's thigh triangle) petechiae can frequently be demonstrated.

In some instances similar erythemas may appear on the shoulders and on the inner aspects of the upper arms. They may be more dense on the vaccinated arm if not too much time has elapsed since the successful vaccination⁴⁷⁸. This erythema variolosum vanishes relatively slowly. It may still be seen in the early

⁴⁵⁴Haaxen F. Aetiologie der Pocken. Arb. R. Leh. u. Adh. 68: 149-163, 123.

⁴⁷⁷Tejrumi M. and Jones S. The Initial Erythema of Smallpox. J. Inf. Dis. 29: 109-113, 1921.

⁴⁷⁸Morawitz C. Variola. Handb. d. H. u. G. 14: 1-443, 423, 1970.

eruption period and it has often been said that the sites of the initial erythema either remain free of pocks or have relatively few. The petechiae seen in the initial rash should not be confused with the rare purpura variolosa.

The end of the third day marks the end of the initial stage and the beginning of the decisive *eruptive period*.

The *variola exanthem* appears first on the face and head. Within three days it invades the trunk and then the extremities. The face is usually the most densely covered part. Areas subject to friction, as the garter and belt areas, or skin which has been irritated by iodine or other irritants, or the macerated folds of the groin, may produce a richer crop of lesions. Face, extremities and trunk, in the order named, show decreasing degrees of density. The abdomen is the

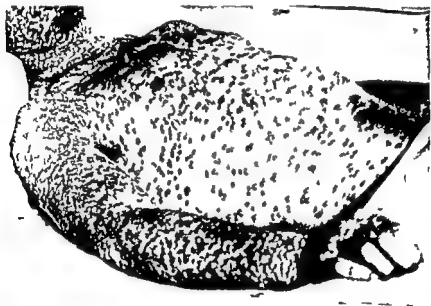


Fig. 52.—Smallpox, ninth day. Severe case with confluent rash in the face. (Courtesy Dr. Max Fox.)

least affected region. However, all these degrees are relative and vary widely with the severity of the case.

The individual lesion, which is accompanied by a slight burning or itching, begins as a pinhead sized papule which grows to a bright red lentil or pea sized efflorescence within one to two days. On the third day of its existence the papule develops a small vesicle on its center which within two more days extends over the whole lesion. Its content changes on the fifth day from the initial clear serum to an opaque fluid and finally to frank pus on the sixth day (ninth day of the disease). This marks the beginning of the pustular stage. The content of the vesicle is under considerable pressure, often giving the palpating finger a firm, shotty sensation. This feature, however, has been overemphasized and it may be entirely absent.⁴⁴ It is not possible to relieve the pressure by needle

puncture, since the vesicle is multilocular. The center of many lesions becomes navel like while the edge appears raised. The pustules are surrounded by a bright red narrow halo. The skin between the pustules is often swollen.

The outbreak of the variola exanthem is accompanied by a sudden drop in temperature after which the patient feels greatly relieved. In mild cases the temperature continues to fall throughout the eruption while in the more severe cases the temperature rises again with or even before the pustulation. The maturation of the pustules takes place in the order of their appearance so that the face is always one step ahead. The duration and the severity of the pustular stage varies. While in some cases the small number and the short lifetime of the pustules may affect the general condition but little a copious or confluent

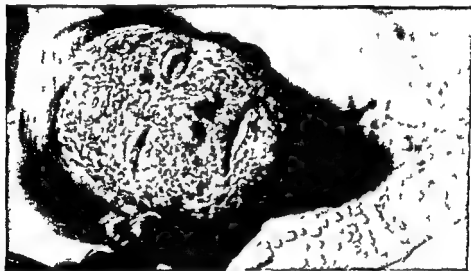


Fig. 53 — Confluent smallpox. (Courtesy Dr. Watson Campbell and Dr. C. A. Newman from Sutton and Sutton, *Diagnosis of the Skin*, The C. V. Mosby Company.)

exanthem causes great suffering with recurrence of high temperature and delirium and all the possible complications of a highly toxic and septicemic state. Skin gangrene not related to bed sores has occasionally been observed. Most of the deaths occur in the suppurative stage. While the widespread inflammation of the skin naturally makes the patient most uncomfortable much of his suffering comes from the mucosal eruptions. The mucosal efflorescence follow the same pattern as the skin lesions papules vesicles pustules. However the roof of the vesicles is destroyed early so that instead of the pustule an erosion develops. The mouth the nasopharynx the larynx and even the trachea down to the bifurcation may be affected. The tonsils become ulcerated by confluent lesions. The tongue is often relatively little involved. The discomfort of the patient is not so much caused by the actual smallpox lesions on the mucosae as by the diffuse catarrhal inflammation which accompanies the exanthem. This is particularly true of the nose and nasopharynx which often are obstructed by bloody crusts

The conjunctiva bulbi is only rarely involved the conjunctiva palpebralis a little more often. Pustules may appear usually in small numbers in the vagina the rectum and the urethra.

The pustular stage at the middle of the second week represents the acme if the disease takes a normal course. From then on the edema of the face subsides and the pus at first in the facial lesions and then in the others in the order of their appearance becomes thicker and the areolae lighter. The pustules which were firm and shotty become flat and shrink. They form yellow crusts which finally become brown dry and loose. The pain subsides however a very annoying pruritus frequently accompanies the loosening and shedding of the scabs. The respiratory irritation subsides and at the end of the second week the temperature is again normal this time to stay. The healing pustules leave pigmentations and pitted scars of varying degree. The scarring may consist of a few pockmarks not much more severe than in some cases of varicella or it may disfigure the patient's face to the utmost for the rest of his life. Diffuse alopecia follows variola probably more often than it follows other exanthematic diseases. The hair grows back except in the few spots where pustules have destroyed the hair papillae.

The clinical picture of smallpox varies considerably with the epidemic and with the status of immunity of the patient. In addition complications may modify the course decisively.

In *variola confluens* as compared with *variola discreta* the pustules are so dense that they coalesce and form large superficial abscesses and infiltrations. All symptoms are aggravated. The face is most severely involved the trunk less so. The eyes cannot be opened the lips and the nose are swollen and crusty and the saliva runs from the mouth. According to an old clinical experience (Sydenham after Osler Christian⁴⁰) the number of pustules on the face decides the outcome and a relatively mild eruption on the rest of the body does not make up for a dense and confluent exanthem on the face. Such confluent cases are sometimes but not always heralded by severe lumbar pain in the initial stage and by a precipitate eruption on the second or third day.

Variola minor is a mild form of variola with a sparse exanthem which does not always start on the face⁴¹. There is no initial rash and no second fever period. All symptoms run a mitigated and abbreviated course. Tièche⁴² often observed a one to two day period without symptoms between the prodromes and the eruption. Very experienced authors believe that *variola minor* is a separate disease but others⁴³ propose a unitarian theory. Some of the arguments follow. No certain case of *variola major* stemming from contact with *variola minor* is known. Vaccination does not afford the same protection against *variola minor* as against *variola major*⁴⁴ although this is controversial.⁴⁵

⁴⁰Immman, H. Vari. III. Vienna 1896. Alfr. d. Hölzer.

⁴¹Tièche, M. F. Epid. mit. gisch. u. med. exp. rim. steller über Variola und Vaccin. Horre p. Schweiz. Arztbl. 1913.

⁴²Bergh (in G.) Vari. II. und Vari. III. Centralbl. f. Bakteriol. 110. 9. 115. 119. 120. 19. 9.

⁴³Van Camp, J. H. et al. Consideration sur le diagnostic de la variola major et de la variola minor. Bull. Offic. Int. Inst. d'Hyg. pub. 27. 1734. 1. 41. 1925.

⁴⁴Röber, F. Beobachtung bei einer Epid. von Variola. Deutsche med. Wchnschr. 40. 793. 94. 1914.

Variola minor does not always immunize against vaccinia (see Sobernheim). The variola minor pustule is white and has several times been described as unilocular and not umbilicated¹¹. Such terms as *alastrim*, *amaas*, *kaffir pox*, *white pox*, and *Cuban itch* have been used to designate the epidemic variola minor. It should be emphasized that if the mild character of a case of variola is due to the status of immunity for example preceding vaccination infections stemming from such cases may be severe. The exanthem may fail to appear after the prodromal symptoms. Such cases of *variola sine exanthemae* are rare usually favorable but also contagious.

Hemorrhagic complications may create two distinct varieties of smallpox. If purpuric symptoms appear in the prodromal stage if the initial rash is purpuric or petechial or if the mucosae show early petechiae or bleeding one speaks of *purpura variolosa* or hemorrhagic smallpox. These patients die within a few days in some instances before the outbreak of the exanthem. Fulminating *purpura* discoloring wide areas may develop. All who have seen such cases of black smallpox have been impressed by the ghastly appearance of the patient whose entire skin may be deep purple the face swollen the conjunctivae deep red and the gums bleeding.

The term *variola pustulosa hemorrhagica* characterizes the cases with the appearance of hemorrhagic symptoms in the pustular stage. This too is a severe and usually fatal complication. At first the halos then the pustules themselves become hemorrhagic. Osler¹² and other clinicians who have witnessed great epidemics of smallpox agree that the earlier the purpuric complications set in the more dangerous they are.

The earlier clinicians¹³ mention two rare peculiar cutaneous variations of the healing process. Sometimes a warty looking crusty greasy mass may remain in the place of the pustule and only slowly become eliminated. This is called *wart pox*, *variola verrucosa*. Still rarer is *variola siliquosa*. Here the content of the pustules disappears rapidly leaving for a while an air filled blister. The gross pathology of the inner organs shows a surprising paucity of changes. The histopathology of the early stages of the variola papule shows acanthosis with vacuolization and liquefaction around a center in the higher strata of the prickle cell layer. Here the multilocular vesicle develops. The umbilication is caused by acanthosis which raises the edges higher than the liquefied center. The navel may disappear if the chambers of the vesicle coalesce or become more distended. The peculiar cell changes described by Unna are identical with those in vaccinia (see under vaccinia).

The diagnosis is occasionally difficult. A secondary syphilid may though rarely imitate variola and one should search for other syphilitic signs or symptoms. Variola if modified by vaccination may resemble varicella. However chicken pox has no prodromes and the temperature does not drop during the eruption which appears in several crops predominantly on the trunk. The vesicle in varicella is very superficial and thin and can be wiped off while this is not possible with the deeper and more thickly walled smallpox lesion. The areola (corona) in varicella is irregular and sometimes very wide while the halo around

the variola pustule is narrow and regular. The shape of the varicella vesicle is often irregular even elongated in the body folds compared with the round circumference of the variola lesion. Deep seated scabs on the palms are quite characteristic of smallpox. The shotty feel of variola lesions may be absent and may occasionally even be found in varicella. In smallpox the axilla often remains free while it is a favorite spot for the eruption of chicken pox.⁴⁶⁵ Morawetz⁴⁶⁷ mentions unusually copious eruptions of erythema multiforme as being a possible obstacle to the diagnosis. Here the emphasis of the distribution is on the extensor surfaces of the extremities not on the face. The prodromal stage the fever, the contacts the preceding vaccinations and especially Paul's test the scarification of a rabbit's cornea with a needle dipped into the questionable lesion establishes the diagnosis (see vaccinia). In persons who have been sensitized by often repeated vaccination a skin test with sterilized material from the questioned eruption may be positive within four hours (Tieche after Paschen⁴⁶⁸) if the disease is vaccinia or variola.

No specific therapy is known. The treatment is symptomatic. Vaccination at the time of exposure attenuates the outbreak of variola to an attack of fever without eruption. A few days after exposure vaccination can still weaken the course but this is no longer true after the outbreak of the prodromes.

⁴⁶⁵Fall & A. Differential Points in Diagnosis of Smallpox and Chickenpox. Ohio State M. J. 24
9:890 1928

CHAPTER VI

SYSTEMIC INFECTIONS

Pinta

Pinta (mal del pinto carate) is a tropical disease characterized by unusual pigmentary changes and caused by *Treponema carateum*. This treponema was discovered by Grau Triana and Armenteros in Habana, Cuba, in 1938. The spirochete for which at least six names exist (*Treponema herrejonii*, *pictor*, *americana*, *pinta*, *dischromeoderma*) is demonstrable in active lesions by the dark field examination or by the same stains which are used to detect *Treponema pallidum* from which it is morphologically indistinguishable. For generations the disease was considered a mycosis. However, the absence of fungi, the high incidence of positive Wassermann and Kahn reactions (Menck ⁴⁶ 60 per cent, Herrejon and Pallares 100 per cent after Pardo Castello and Ferrer ⁴⁷) and the rapid response to antisyphilitic treatment made a spirochetal cause of the infection appear probable. The disease is inoculable into normal and syphilitic persons but not into persons with pinta of the later stages (León y Blanco ⁴⁸, Beerman ⁴⁹). It is believed that the infection takes place by contact and not by a vector. No venereal transmissions have become known. The infection conveys immunity. The disease occurs predominantly among colored races in the Latin American countries. About 600,000 sufferers are believed to live in Columbia and over 270,000 in Mexico ⁴⁰. A few cases have been discovered among Negroes in Chicago ⁴¹.

Dermadromes.—Mainly through the brilliant and heroic work of the Cuban dermatologists it is now known that seven to ten days after an inoculation of pinta material into the skin a minute *primary papule* with a red halo develops. Within two months this initial lesion gradually becomes an erythematous squamous patch surrounded by satellite papules which tend to coalesce with the primary lesion. The primary patch may grow slowly to 10 to 13 cm. in diameter and finally become indistinguishable from secondary lesions (pintids, León y Blanco ⁴²).

⁴⁶Menck W. P. Reactions of Positive Wassermann Reactions Associated with Various Diseases. Fifteenth Annual Report of the Medical Department of the United Fruit Company, New York, 1925.

⁴⁷Pardo Castello A. and Ferrer J. Pinta, mal del pinto carate. *Arch. Dermat. & Syph.* 48: 643-644, 1942.

⁴⁸León y Blanco J. Las 10 casadas palmarenses y pinta en el mal del pinto. *Rev. d. med. trop. y parasitol. bacteriol. clín. y lab.* 6: 16, 1942. Estudio epidemiológico del mal del pinto en una pequeña aldea del estado de Guerrero (México). *Rev. d. med. trop. y parasitol. bacteriol. clín. y lab.* 6: 19-20, 1942. Las reacciones de Border Wassermann y de Kahn en el período secundario del mal del pinto. *Rev. d. med. Trop. y parasitol. bacteriol. clín. y lab.* 6: 201-20, 1942. Nota sobre la evolución histórica de nuestros conocimientos acerca del mal del pinto o carate. *Rev. d. med. trop. y parasitol. bacteriol. clín. y lab.* 6: 29-30, 1942.

⁴⁹Beerman H. Pinta: Etiology and Clinical Studies. *Am. J. M. Sc.* 208: 611-6, 1913.

⁴⁰For II. A Cause of Mal del Pinto in Mexico. A. B. Derm. & Syph. 21: 22-23, 1935.

L. Berthel E. Pinta in the Continental United States. *J. A. M. A.* 122: 619-621, 1943.

which appear five to twelve months or more after the infection. A variety of pintids characterized as trichophytoid, psoriasiform, lichenoid and eczematoid have been described. The lesions are at first pink, then red, purple and finally slate colored, indicating the onset of the pigmentary changes which are so characteristic of the disease. The older secondary lesions often show a depressed



Fig. 54.—Pinta. Typical triangular leukoderma of volar aspect of the hands. (From Jardo-Castillo, Arch. Dermat. 1942.)

center and an active raised margin. Coalescence of the lesions is a feature. The distribution becomes more and more symmetric and widespread and the pintaids may involve any region although they are found mostly on the exposed areas and over the bony prominences. There are hardly any subjective sensations. In Mexico the early secondary stages were called *empeines*. They were thought to be a separate entity. Their relation to pinta has only recently been elucidated by León y Blanco⁴³⁸ (see Pardo-Castello⁴³⁷).

The secondary stage gradually passes into the *tertiary* or *dyschromic* stage with the spectacular pigmentary symptoms which have given rise to the name *mal del pinto* (Spanish *pintar* to paint meaning piebald disease). The first dyschromic lesions may appear after one year especially in symmetrical distribution on the hands, forearms, feet and lower legs. However the face, the trunk and the scrotum may finally be covered with permanent vitiligo-like changes.



Fig. 55.—Pinta. Hyperkeratotic and dyschromic lesion of the palms. (From Pardo-Castello 1942.)

Especially characteristic is a depigmented area on the volar aspect of the wrist in the shape of a triangle with the base bordering the palm and the apex pointing toward the elbow. Such lesions are composed of irregular sharply outlined spots of hyperpigmentation which in white persons who are rarely affected varies from yellow to brown and in colored persons from brown to slate blue and black, the center being white. Pardo-Castello⁴³⁷ emphasizes the pepper and salt or mottled arrangement of the pigmented lesions. The discoloration may be found accompanied by follicular and diffuse keratosis and areas of atrophy.

The Wassermann is always positive in this stage. The white patches represent the final stage and do not respond to antisyphilitic treatment which is effective in the other lesions.

The general health seems little affected during this extremely chronic disease which may last several decades. However it is likely that as in syphilis more internal manifestations will be discovered. Already a high percentage of late cardio aortic lesions and spinal fluid changes have been reported.⁴⁰

The initial and secondary lesions show essentially the same histological changes that is edema of the rete and inflammatory infiltration. The great disturbance of the pigmentary physiology is expressed by the lack of pigment in the basal layer and great accumulations of melanophores in the cutis. Spirochetes are numerous only in active lesions. Late lesions become increasingly atrophic.

The differential diagnosis includes syphilis, yaws, vitiligo, leprosy and certain dyschromic conditions. Seroreaction, the finding of spirochetes and the effect of specific treatment will help. However the differentiation from syphilis and yaws will rest mainly on the clinical appearance. The effectiveness of the same treatment in all these diseases reduces the practical importance of the differential diagnosis.

Frambesia (Yaws)

Frambesia is a tropical spirochetosis closely related to syphilis although different in many ways. The word frambesia derived from the French framboise raspberry refers to the red papillomatous lesions which are a conspicuous feature. The disease is called yaws in English, le pian in French and la boubarole or boubas in the Caribbean area. The causative agent is *Treponema pertenue* a spirochete which is morphologically indistinguishable from *Treponema pallidum*. The infection is endemic among the lower classes of all tropical countries, the incidence depending upon the unsanitary conditions rather than on the race. Contrary to a widely held belief that frambesia is predominantly a disease of the colored population it is certain that poor living conditions cause a high percentage of infections among the white population.⁴¹

Transmission occurs chiefly by direct contact. The fly *Hippelates pallipes*, culex mosquitos or leeches possibly play roles as mechanical vectors. Venereal contagion is extremely rare due to the infrequency of superficial mucosal lesions. However penile primary lesions have been observed⁴² and are even considered very common in the Cameroons.⁴³ Congenital infection is questioned by many authors although claimed by some. Infection with yaws seems to immunize against syphilis.⁴⁴

The incubation period lasts two to three weeks during which time mild febrile prodromes often occur.

⁴⁰Saenz H, Triana J and Monteros J. Pinta in Cuba. Arch. Dermat. & Syph. 41: 463-479 1940.

⁴¹Pardo-Castello A. Frambesia 500 Cases Arch. Dermat. & Syph. 40: 762-775 1939.

⁴²Mayr M and Nauck E G. Framboesie Hautb d H u Gk 12: 837 1932.

⁴³Hallenberger. Framboesia Arch f Schiffs u Tropen Hyg 20: B (heft 3) 1916.

⁴⁴Fox H. Skin and Tropical Diseases. New England J Med 221: 48-485 1944.

Dermadromes—The *primary lesion* called the mother yaw appears usually on the exposed parts of the legs or much less frequently elsewhere. The initial sore starts as a papule or pustule which soon becomes granulomatous or ulcerative. Such lesions may disappear or become inconspicuous among the great number of almost identical secondary lesions. In a considerable number of cases the primary lesion keeps on growing and develops slowly into an enormous destructive ulcer. Such "mother yaw" lesions have been seen to remain active as long as twenty years. They may heal with a scar in any stage or may extend peripherally and deeply even to destruction of the underlying bones.⁴⁹³



Fig. 6.—Yaws. Early papulohyperkeratotic plantar lesions. (From Parlo Castello & Arch. Dermat. 1939.)

Multiple primary lesions and the appearance of satellite papules around the sore are well known.

From six to nine weeks after the infection the *secondary eruption* appears. This is a papular rash often ushered in by prodromal symptoms like fever, muscular pains and headache. There is a generalized lymphadenopathy (Baermann

after Mayer and Nauck⁴⁸⁴) The secondary exanthem has a peculiar tendency to develop luxuriant papillomatous lesions These efflorescences may be generalized grouped about the body orifices numerous or scanty small or large They may appear as military pin point sized elements as impetigo like crusty lesions or as raspberry like papillomatous granulomas^{483 486} Most of the secondary lesions disappear but groups of papules arranged in rings (ringworm yaws) or in lichenoid plaques persist during the late secondary period The soles are often covered with symmetric deep cornlike painful papules which are surrounded by keratotic eczematoid scaly skin (crab yaws) (Fig 56) The truly granulomatous and frambesiform nature of such plantar lesions becomes evident after removal of the thick horny top layer⁴⁸⁷ On the palms such lesions may look psoriasiform Areas of mottled pigmentation and depigmentation on the hands and feet may create a picture which closely resembles pinta⁴⁸⁸ (Schuffner's picture in Mayer and Nauck⁴⁸⁴)

The tertiary lesions are seen earlier than in syphilis A period of late secondary latency is rare As in syphilis the late lesions may be ulceroserpiginous sometimes of enormous size with a nodular border and a scarred center or deeply destructive and granulomatous They may destroy joints and bones and cause pathological fractures Particularly horrifying are the facial and nasopharyngeal mutilations known as *gangosa* which may cause complete loss of the nose and may extend to the lips and lay open the nasal and oral cavities Later on scarring may cause microstomia and the hands under similarly destructive and cicatrizing processes may become monstrously deformed and mutilated Pardo Castello⁴⁸⁹ emphasizes the bone destructive tendency of yaws in contrast to the more osteoplastic nature of the corresponding syphilitic processes

There is remarkably little involvement of the mucous membranes Destruction of the soft palate is rare and cardio aortic and cerebrospinal changes are infrequent⁴⁹³

The pathology of yaws largely follows the pattern of syphilis The proliferative tendency of the papules which in syphilis manifests itself in the condylomata is much exaggerated in yaws

Yaws apparently renders the patient immune and there seems to be some degree of cross immunity in the later stages of syphilis and yaws

Treponema pertenue is demonstrable in many of the lesions and occasionally in the late gummatous processes which in syphilis is only extremely rarely the case Wassermann Kahn and the related reactions are positive in 100 per cent of the secondary cases less often in the later stages⁴⁹⁴ The disease is inoculable into monkeys and like syphilis into the anterior chamber of the rabbit eye and into the testicles of the rabbit

The treatment is largely the same as for syphilis with the emphasis on the arsphenamines and bismuth Mercury and iodine are reported to be unfactorial Oral arsenicals for example acetarsone are effective and convenient

⁴⁸⁴ Schuffner W Die Spirochaeta pertenue und das klinische Bild der *Frambesia tropica* München med Wchnschr p 1364 1907

under primitive conditions⁴⁹³ The treatment consists of daily doses of 0.25 Gm for twenty days These courses are repeated several times after intervals of two weeks Penicillin has shown promising results⁴⁹⁴

Juxta-articular Nodes

Subcutaneous movable pea to walnut sized or occasionally much larger nodules of firm or hard consistency occur on the extensor and lateral surfaces of the elbows knees and other joints⁴⁹⁵ They grow slowly for years usually sym-



Fig. 57—Juxta-articular nodes (Courtesy of Division of Dermatology Department of Medicine University of Chicago)

metrically often multiple never in large numbers The lesions called juxta-articular nodes are tender in the first years of their development but later are painless and stationary There is no tendency to ulcerate or to heal spontaneously The affected are as a rule elderly persons

⁴⁹³Whit hill and Austrian Treatment of Yaws With Penicillin Bull Johns Hopkins Hosp 75 23 740 1944

⁴⁹⁴Zakon J. J. and Allen H. B. Juxta-Articular Nodes Quart Bull Northwestern Univ Med School 11 2 6-723 1940

The pathologic picture ³⁰⁰ (Jernselse after H. Hoffmann¹¹⁰) is that of a cyst with a thick fibrous vascular outer wall in which perivascular inflammatory reactions with foreign body type giant cells and proliferation of blood vessels dominate. Toward the center of the cyst the inflammation subsides, the elastic fibers deteriorate, and the nuclei lose their stain. The center is a mass of hyalin or liquid degenerated material.



Fig. 53.—Syphilitic juxta-articular nodule. (From I. Salz F. Arch. Dermat. 1945.)

The nodes are rare in temperate zones and common in the tropics. This is due to the fact that the tropical treponemal diseases, especially yaws⁴⁹⁴ but also syphilis^{110 300 301}, pinta⁴⁹⁵ and bejel³⁰² are apt to cause juxta-articular nodes in their later stages. Spirochetes were demonstrated regularly in the nodes of thirty-six patients with framboesia^{300 302 303}. Patients with active lesions should receive antisyphilitic treatment.

Besides the treponemal diseases, several disorders, particularly chronic arthritis, may sometimes cause typical juxta-articular nodes^{110 121 304}.

Relapsing Fever

A group of relapsing fevers is characterized by attacks of severe acute fever lasting two to ten days.⁴⁹⁶ The causative organism *Borrelia recurrentis* (*Spirochaeta obermeieri*) discovered in 1868 is a very large spirochete about six times the length of the diameter of a red blood cell and is found in great numbers in the blood during the attacks. It is transmitted by lice, bedbugs (Ticin after Eggebrecht³⁰⁵) and ticks,³⁰⁶ probably not by bite but by inoculation from the crushed infected insect body with the scratching nail. There are a number of

³⁰⁰Jernselse H. Über syphilitische Juxta-artikuläre Knotenbildung. Arch. f. Dermat. u. Syph. 132:157, 1906.

³⁰¹Salz F. and Newton D. L. Syphilitic Juxta-Articular Nodules. Arch. Dermat. & Syph. 48:65, 1913.

³⁰²Hudson F. H. Yaws and Syphilis. Am. J. Trop. Med. 21:345-355, 1931.

³⁰³Van Dyk and Oudendal. In: The Histology and Cause of Juxta-Articular Nodules. Geneesk. tijdschr. v. Nederl. Indië 88:417, 12.

³⁰⁴Kravitsky A. and Bulvahter V. Syphilitic Infection and Syphilitic Juxta-Articular Nodules. Soviet Voenik Dermat. 3:16, 1933. Zitiert 39:463.

³⁰⁵Eggebrecht E. Festschrift. Vienna, 1900. Alfred Hödl.

³⁰⁶Schilling C. Rückfallfieber in Ha. Thuch. d. Intern. Medizin. Vol. II. Berlin, 1905. Julius Springer.

geographic varieties of relapsing fever differing in vector duration and number of attacks. The relapsing fevers are important in Europe and Africa less so in America where there are some endemic foci in California and Nevada⁵⁰⁷. The first attack starts abruptly after one to seven days of incubation. There may be prostration often vomiting cough splenomegaly and increasing anemia. The attack ends by crisis and the patient recovers remarkably quick but after one to two weeks he has another though often milder attack. Such bouts may recur two three or even five times. The prognosis is good the fatality rate in most epidemics is less than 5 per cent.

Dermadromes —Dermadromes are inconspicuous and inconstant. There is a decided icteric tendency which together with the increasing anemia may create a dirty grayish brown color. This facial browning was emphasized by the older authors⁵⁰⁸ (McCormack after Eggebrecht⁵⁰⁹). With varying frequency in different epidemics rose spots similar to those in typhoid morbilliform and very rarely scarlatiniform and miliary rashes⁵⁰⁸ have been noticed. The relapsing fever roseola is described⁵⁰⁹ as appearing at the end of the first attack most frequently on the lateral surfaces of the trunk on the back on the extensor surfaces of the elbows and about the wrists. Face and legs remain free. The spots are smaller than those in typhoid round purely macular and pink to red in color. They fade after about one hour but since they do not appear simultaneously these spots are visible for a much longer period. The exceedingly ephemeral character of the spots is stressed by other authors⁵¹⁰. In ten years of experience with American relapsing fever in Nevada Parsons did not notice any rashes (personal communication).

Since the diagnosis rests on the finding of spirochetes in the blood the infrequent exanthems are hardly of diagnostic importance. The usual symptoms accompanying profuse sweats sudamina and mild desquamation are common. *Herpes* was noticed in up to 30 per cent of the cases in certain epidemics. *Petechiæ* (which should not be confused with flea bites) and other hemorrhagic symptoms especially nosebleed occur⁵¹⁰ occasionally especially at the end of the attack. It is interesting that the acumen of the older clinicians did not fail to notice that patients with relapsing fever usually show the excoriations pigmentations and pyodermatic infections connected with chronic pediculus and neglect a state known as *lagabond's skin*.

Specific treatment consists of a few injections of arsphenamine.

Weil's Disease (*Leptospirosis ictero-hemorrhagica*)

Weil's disease (*Leptospirosis ictero hemorrhagica*) is an acute spirochetial infection with fever gastrointestinal and hepatic symptoms and prostration. After five to six days of high temperature a large percentage of the patients become jaundiced and hemorrhagic tendencies become manifest. The mortality

⁵⁰⁷Morrison G. B. and Parsons L. Relapsing F. J. A. M. A. 116: 220-221 1911.

⁵⁰⁸Strong R. F. Relapsing Fever. C. B. North America 27: 731-744 1913.

⁵⁰⁹Ottlinger J. and Halbrech J. Fph. mere Roseola beim Rückfall der Mönch. n. med. Wchn. schr. 69: 774-779 1922.

amounts to about 12 per cent with most of the deaths occurring around the end of the second week

The causative spirochete is found in the blood

Dermadromes—Frequent skin manifestations include icterus and hemorrhagic lesions. Scarletiform urticarial⁴¹⁰ and other types of rashes are rare. Non angry endogenous bulbar conjunctivitis and epidercleritis are considered early and striking symptoms⁴¹¹

There are milder varieties of *Leptospirosis* for example the so called inundation or mud fevers in Germany in which morbilliform rashes occur^{412 413}

Ratbite Fever (Sodoku)

There exist two clinically similar diseases which develop in man after the bite of rats but which are attributed to different microorganisms. One of these caused by *Streptobacillus moniliformis* has been discussed under the heading Haverhill fever. Under the name of sodoku which in Japanese means poisoning by a rat the other has been known for centuries only in Japan although it is as cosmopolitan as the rat. Simultaneous infection with both microorganisms occurs^{413 414}

The cause of sodoku *Spirillum minus* (formerly *spirochaeta morsus muris*) was discovered in 1917⁴¹⁵. It is a fast moving spirochete having only two to five spirals and shorter in length than the diameter of a red blood cell. There are flagella at both ends (B. McDermott after Beeson⁴¹⁶)

A great number of cases with the spirillum present have been reported from many countries. In a great number of the cases children were affected⁴¹⁷. Epidemics are not known. The disease is rare one case being recorded among 20 000 hospital admissions in Kansas City. Yet because of its wide use in the treatment of general paresis the symptomatology of the disease is well known.

Spirillum minus is harbored by rats especially the vicious *rattus norvegicus* but also in a host of other rodents and occasionally by cats and dogs. White mice and guinea pigs are susceptible to laboratory inoculation. Animal inoculation with blood taken at the height of a febrile paroxysm is the most reliable method of demonstration⁴¹⁸. No pure cultures have been grown so far. The organism may occasionally be demonstrated in the serum from a primary lesion in a local lymph node or in the blood⁴¹⁹ with the help of the dark field or with

⁴¹⁰Lorenz O. Jr. Studies in Wells Disease. U. S. Nav. M. Bull. 42, 560-566, 1914.

⁴¹¹Jathe J. Schlammler ber Fröhen ber Wass. III ber Felds ber Infektion durch Leptospirose. Med. J. 35, 1133-1139, 1939.

Rimpau. Fildflebe. Münch. med. Wchnschr. 85, 1977-1979, 1938.

⁴¹²Nathan H. Rattenbisskrankung. Zbl. Chir. pp. 7, 759, 1933.

⁴¹³Anderson N. P. A. I. Specto. B. I. Rat Bite Fever Associated With Sporothrix. J. Infect. Dis. 60, 314-319, 1935.

⁴¹⁴Putaki I. Tokaki T. Taniguchi T. a. d. Oumi G. The Cause of Rat Bite Fever. J. Exp. Med. 23, 47-50, 1916.

⁴¹⁵Beeson P. H. Rat bite fever due to *Spirillum minus*. J. A. M. A. 123, 33-331, 1933.

⁴¹⁶Brüning H. Sodoku (Rattenbisskrankheit) bei Kindern. Ergebn. d. inn. Med. u. Kinderh. 44, 1-44, 1933.

⁴¹⁷Francis E. Rat bite fever and Haverhill fever. J. Am. Tr. A. Am. Physicians 47, 143-151, 1932.

Rogliano A. E. Two Cases of Rat bite fever. Surg. 11, 632-635, 1914.

In some cases severe sensory or motor nervous symptoms prevail. Diffuse and patchy *alopecia* has occurred in later stages. The hair grew back after general improvement.⁵⁴

The *Wassermann reaction* and related tests become positive in 50 to 60 per cent of the cases.⁵⁵

The mortality of the treated patients is low. No fatality occurred among 125 cases reported in the United States.

The clinical diagnosis must take into account a great many fevers although the history of a rat bite, the primary lesion and the laboratory findings will secure the diagnosis. The differentiation from rat bite transmitted Haverhill fever is made by the laboratory findings⁵⁶ as well as by the presence of arthritis and the lack of a pronounced primary chancre in Haverhill fever. Haverhill fever after rat bite is probably more common than sodoku.

Specific treatment consists of from three to ten injections of neoarsphenamine or similar arsenicals. Bismuth is also effective.⁵⁷ The first administration of specific drugs may be followed by a Herxheimer reaction.⁵⁸ Recurrences have been seen after less than three injections.

The therapeutic inoculation of the disease into patients with general paresis instead of malaria was done in a great number of patients but has been abandoned because complications occurred and control of the infection often proved difficult.

African Trypanosomiasis

The trypanosomiasis of central Africa (sleeping sickness)⁵⁹⁻⁶² is caused by the flagellates *Trypanosoma gambiense* and *Trypanosoma rhodesiense*. These microorganisms are blood parasites of many wild and domesticated large mammals for example oxen, sheep and antelopes and are transmitted to man by the bite of the tsetse fly *Glossina palpalis*. The transmission is cyclical and mechanical. The trypanosomes are most abundant in the blood during the febrile attacks but they are also found in the lymph nodes, the cerebrospinal fluid and serous fluids. They can be stained, demonstrated by dark field and cultivated on salt agar (NNN medium).

The disease is endemic and at times epidemic in large parts of equatorial Africa especially around lakes and along rivers where the tsetse fly lives. At times the population of large areas is decimated by the disease which affects the colored races as well as the white. The infecting bite is often immediately or within one week⁶³ followed by local inflammation. These primary chancres do not develop invariably but furunculoid and ulcerative lesions with regional

⁵⁴Cahill and A. Rat bite fever Proc Roy Soc Med 27 157, 1934.

⁵⁵Ozaki, Y. Rat bitekrankheit Isolierungsmethod. des B. reg. Jap. J. Dermat. Urol. 32 46 193. Zitiert 344.

⁵⁶Manson Bahr P. H. Manson's Tropical Diseases London 1939 Cassell & Co. Ltd.

⁵⁷Illersberg F. R. African Sleeping Sickness M. Ch. North America 27 83, 1947 1943.

⁵⁸May M. Hautreaktion nach exotischen Krankheiten. Trypanosomiasis Handb. H. 11 u. Ch. 12, 1 180-185 1932.

⁵⁹Graf H. Beitrag zur Pathologie des Glossina palpalis-Stiches und der Inkubationszeit bei Schlafkrankheit Arch. f. Schiff- u. Tropen Hyg. 32 219 220 1939.

lymphatic involvement, fever, and the local presence of the trypanosomes have been observed beyond doubt.^{5, 9, 331, 33, 333} About two to three weeks after the infection, the patient is stricken with fever of varying intensity and course, the



Fig. 59.—*African trypanosomiasis*. Secondary anthrax. (From L. Owen, courtesy The Annals of Tropical Medicine and Parasitology, The University Press of Liverpool.)

irregularity being a diagnostic feature.^{5, 9} The patient becomes weak and anemic and his mental abilities suffer. General lymphadenopathy is a constant though varying feature, with the lymphatic nodes at first being soft later hard. Head

³³¹Géry, L. R. Les phénomènes cutanés au cours de la trypanosomie humaine en particulier dans la race nègre. *Thèse de Paris*, 1910.

aches, paresthesias and a peculiar kind of deep hyperesthesia on knocking against a hard object known as Kerandel's sign indicate the early nervous involvement.

Dermadromes—The primary lesion has a deep red center surrounded by a pearly white vesicular zone and a red halo.⁵³ Erythema and infiltration around the bite may persist far into the secondary stage. The bite however differs in its appearance from the more transitory *secondary eruptions*.^{521, 525} Characteristic of the early secondary stage but not present in all patients nor at all times⁵³⁶ are *urticarial erythemas* in large round patches, rings or crescents which have a decided tendency to spread peripherally and heal in the center. Coalescing circinate rather large patterns may cover the entire back.^{532, 537} These trypanids are of unpredictable and fugitive nature. They may be without change for days or even several weeks and then they may evanesce quickly reappearing in other places. The erythemas are slightly raised but not or little infiltrated.^{531, 538} Pink in color of normal temperature, often sensitive and sometimes very itchy especially if they are of a more exudative papular type.⁵³⁶ Erythema nodosum occurs.^{5, 9, 533} The blood taken from lesions contains more trypanosomes than the peripheral blood of the other skin. The relatively delicate erythema is difficult to detect in colored skin.* In some cases the erythema is annular and linear⁵³⁸ like the erythema annulare encountered in rheumatic fever.

Localized edema especially of the face is common in the secondary stage.^{533, 534} Another dermatome is a vascular bluish mottling independent of the erythemas (Master after Mayer⁵).

The fading skin lesions do not leave any trace.⁵³⁶ The secondary stage may last a long time, seven years usually being considered the maximum. The skin manifestations become less marked and less frequent and gradually the disease drifts into the sleeping sickness stage with deep mental changes, stupor and somnolence during daytime, restlessness at night, muscular twitchings, tremor and convulsions. Hepato-splenomegaly is present. If not treated death in profound cachexia is inevitable.

During the *encephalitic* stage early features including erythema may still be present. The gross pathology is meager. Microscopically perivascular round cell infiltrations can be seen throughout the brain and especially in the erythematous skin.⁵³⁹

The *diagnosis* rests on the finding of trypanosomes in the blood, in the lymph node material or in the spinal fluid. The clinical diagnosis of trypanosomiasis

D. H. R. Berger of the American Mission to Lepers who has had an almost unique experience with African trypanosomiasis does not believe that the rash is very commonly seen in the case of the patients in the treatment centers but that the rash is advanced cases and the color of the skin makes the erythemas difficult to observe in persons of color.

⁵² Ruge H. Sleeping Sickness. Med Welt 12: 1485-1488, 1939.

⁵³ Ch. Valli, R. P. and Lévy G. Un cas de trypanidose éruption précoce de la maladie du sommeil. Bull Soc française de dermat. et syph 35: 165, 1934.

⁵⁴ Darré H. Les symptômes cutanés de la trypanosomie humaine. Ann de dermat. et syph 9: 673, 1908.

⁵⁵ Owen H. L. Clinical Notes. Trypanosomia in Ann Trop Med 22: 47-50, 1938.

⁵⁶ Audry C. Erythème annulaire centrifuge et trypanosomie. Bull Soc française de dermat. et syph 39: 185-186, 1932.

may be extremely difficult especially in persons who have moved from Africa to other countries. The large erythematous urticarial centrifugal and annular erythemas are a most valuable sign. Together with internal manifestations they are almost diagnostic. Arsenic as tryparsamide (pentamidine (M & B 800) and naphuride (Breyer 205 germanin) are considered of high value.

American Trypanosomiasis (Chagas' Disease)

American trypanosomiasis is caused by *Trypanosoma cruzi* and transmitted from infected persons and reservoir animals (armadillo opossum) by various species of *Panstrongylus* *trialoma infestans* and other bugs.



Fig. 80—Chagas' disease. Primary lesion (inoculation chagoma, fourteenth day). (Courtesy Melion de Estudios de Patología Regional Argentina, Jujuy, Argentina.)

Skin Manifestations have long been considered of little importance. Recently, however, Mazza and his associates⁵³⁹⁻⁵⁴⁷ demonstrated their significance.

⁵³⁹Mazza S and Prieto H. Manifestaciones cutáneas en la inoculación (Chagomas) y hematológicas en enfermedad de Chagas. Universidad Buenos Aires. Melion de Estudios de Patología Regional Argentina (Jujuy). Publ. a. 10. 46 pp. 3-7. 1910.

⁵⁴⁰Mazza S and Prieto H. Chagoma de inoculación a guiso de esputo otrapa de morbiliforme. Ibid. Publ. 46 pp. 55-56. 1910.

⁵⁴¹Mazza S and Prieto H. Chagoma de inoculación y esputo otrapa de morbiliforme. Histopatología. Ibid. Publ. 46 pp. 85-101. 1910.

⁵⁴²Mazza S, Basso G, Basso H, and Conte H. Chagoma antirreticular chag. multiples metastaticas y hematologicas complicadas oftalmoganglionar. Ibid. Publ. 46 pp. 105-118. 1910.

⁵⁴³Mazza S, Basso G, and Jörg M. F. Chagomas hematologicas. Ibid. Publ. 47. 1910.

⁵⁴⁴Mazza S and Jörg M. F. Chagoma experimental. Ibid. Publ. 47. 1910.

⁵⁴⁵Mazza S and Jörg M. F. Investigación de la enfermedad de Chagas. Ibid. Publ. 4. 1910.

⁵⁴⁶Mazza S. Esputo otrapa de morbiliforme en enfermedad de Chagas y otras manifestaciones erupivas. Ibid. Publ. 71.

⁵⁴⁷Mazza S and Araniz C. A. Fisiología y fisiología de la enfermedad de Chagas. Arch. Fisiología u Trop. Hyg. 25. 553-561. 1931.

in a series of important investigations. A primary skin lesion may appear as a large dark red prominent and deeply infiltrated nodule with or without intact epidermis (inoculation Chagoma) which is histologically characterized by fat necrosis. Lymphangitis follows the primary lesion. The inoculation often occurs on the face especially about the eye. Thus the first symptom often is a bilateral unilateral edema with conjunctival injection. This eyelid edema lasts about four weeks (Romana's sign).



Fig 61—Chagas disease. Unilateral and bilateral edema and conjunctivitis (Romana's sign). About three weeks after infection. (Courtesy Misión de Estudios de Patología Regional Argentina, Jujuy, Argentina.)



Fig 62—Chagas disease. Rash five days old. (Courtesy Misión de Estudios de Patología Regional Argentina, Jujuy, Argentina.)

As early as five days after the infecting bite a papular rash in the neighborhood of the bite a generalized circinate morbilliform or scarlatiniform erythema and cutaneous and subcutaneous nodules some of large size have been observed. These nodules are very firm and deep red if they arise from the more superficial strata. Mazzia also describes impetiginous and ulcerative eruptions seen several months after the infection.



Fig. 63.—Chagas disease. Rash five days old. (Courtesy Mission de Estudios de Patología Regional Argentina, Jujuy, Argentina.)

Since the thyroid is often affected in the later stages dermadromes which occur in myxedema may be encountered. Edema of the face and skin and also bronzing are mentioned. The South American authors consider treatment with Bayer 7602 of great value but the drug the formula of which is secret still lacks general recommendation because of the danger of nephritis.²⁴¹

A skin test with a cruzin has been developed*. The diagnosis however rests mainly on the microscopic and cultural evidence of trypomastotes in the patient's blood.

*May and Pifano. Abstract of Trop. Dis. Bull. 29, 90, 1942.
²⁴¹Mackie, Th. T., Hunt, G. W. and Brookes, W. G. (1941). A Manual of Tropical Medicine. Philadelphia, 1945. W. B. Saunders Company.

Leishmaniasis

The leishmanias are flagellated protozoans which are capable of producing a group of diseases which are all of dermatological interest. Two of them, oriental sore and American leishmaniasis (espundia) and possibly a third disease, tropical granuloma inguinale, are predominantly skin diseases and therefore will not be discussed. *Visceral leishmaniasis* or *Kala-azar* however, is an internal disease with specific skin manifestations. It occurs in an infantile and in an adult form which are closely related.

The causative protozoan is a small ovoid or round body found either free or in cells of the reticulo endothelial system, particularly in the spleen, the liver and the bone marrow. In cultures on blood or salt agar (NNN medium) they assume the characteristics of flagellates and are inoculable into dogs and monkeys. The disease is endemic in the Mediterranean and the Near and Middle East, especially in India, which has been visited by great epidemics. Sandflies (*Phlebotomus*) are now considered as vectors, with dogs as a reservoir, particularly in the Mediterranean area.



Fig. 61.—Lost kala-azar (terminal leishmaniasis) in an incompletely treated case of visceral kala-azar. Depigmented nodules on the face. (Courtesy Dr. S. K. Ghosh Dastidar.)

The incubation period is over ten days; long latency may occur. Mirzozian⁴⁴ claims to have found the primary lesion in inconspicuous, lentil-sized papules on the faces of children, who several months later showed secondary symptoms of infantile kala-azar. The lesions, which contain leishmanias, may still be present at the time of the outbreak of systemic symptoms or they may have healed and left pigmented spots. The onset is insidious or abrupt, with spiking fever, which

⁴⁴Mirzozian, N. A. Primary Lesions of Visceral Leishmaniasis in Children. *Trop. Dis. Bull.* 40: 295-296, 1943.

may last many weeks. Then an afebrile period with improvement may occur followed by a relapse of fever. After several attacks a chronic state of emaciation, low temperature and anemia becomes established. Gradually the liver and spleen enlarge to tremendous size—the big protruding abdomen contrasting sadly with the thin limbs. The appetite remains good for a remarkably long time. Unusually low leukopenia and later ascites and edema are common. Death is caused by cachexia or intercurrent disease, for example, dysentery or noma. The microscopic pathology shows abundant leishmanias in the reticulo endothelial system.

Dermadromes—The skin gradually takes on a claylike gray or dusky color, especially on the hands and feet. This mixture of pallor and pigmentation is seen in white as well as in colored races.³³¹ The dusky color accounts for the

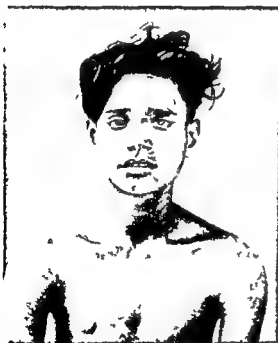


Fig. 65



Fig. 66

Fig. 65—Lost kala-azar small leishmaniasis in a person of dark complexion. Small nodules on the partly depigmented areas on the chin, from one of which *Leishmania donovani* could be demonstrated in the smear. Sharply defined pigmented spot or scattered over the chest, shoulders and face. Patient had visceral kala-azar one year ago and was treated with 7 Gm. of ureastilamine, which is much less than the therapeutic dose. (Courtesy Dr. S. I. Ghosh Dastidar.)

Fig. 66—Noma as a complication of kala-azar. At nasal puncture smear showed *Leishmania donovani*. (Courtesy Dr. S. I. Ghosh Dastidar.)

name kala-azar, meaning black fever. Petechiae and other hemorrhagic lesions, especially bleeding gums, are common. With the progressing cachexia, small ulcerations about the elbows and knees, and occasionally larger ulcerations along the legs may develop. Specific papules and gangrenous ulcers containing leish-

mania occur⁵⁵⁰ as well as secondary cachectic ulcerations, such as noma. A most interesting cutaneous form of kala azar^{551 55 553} has become known as the *post kala azar leishmanid*. Eighty per cent of the patients were known to have had kala azar and to have been treated with antimony. Of the rest (Napier after Mayer⁵⁵¹) a previous kala azar infection could be assumed. The eruption starts with erythematous or depigmented patches on the face especially about the nose and mouth. Such macules resembling leprosy may later appear on the limbs and on the trunk (see colored illustrations in M. Mayer⁵⁵¹) but the chin, the upper lip, and the eyebrow region are most frequently and most heavily involved. The macules are often followed by nodules which however may also appear first. These nodules are pea sized or a little larger semiglobular firm nonulcerating and covered with atrophic skin. Their color at first is red later becoming decidedly orange. They may coalesce and form ridges of tuberos lesions which resemble xanthoma tuberosum multiplex. The nodules contain only few leishmanias mostly in giant cells in the center of a granuloma consisting mainly of macrophages and fibroblasts. The hypothesis has been advanced that some possibly antimony fast leishmanias remain in the skin and cause the local recurrences.

The *diagnosis* of kala azar may be suggested by the geographical location and the resistance of the fever to quinine. The finding of leishmanias by splenic or sternal puncture is diagnostic.

Kala azar is *treated* with antimony compounds. The post kala azar leishmanid does not respond well to this drug. It may become arrested in the late xanthomatoid form and remain without changing.

Malaria

There is no cutaneous lesion invariably or even frequently connected with malaria. Physicians of malaria free countries are inclined to visualize the malaria patient as having a sallow skin. This is only occasionally true. In countries where malaria occurs usually a high percentage of the population is infected and suffers from attacks. However the typical *malarial color* a dirty yellowish brown sallow hue which in relatively rare instances may gradually take on deeper shades with a greenish component is rare. The yellowish discoloration is more pronounced immediately after an attack and may approach a bronze shade as in blackwater fever.

Diffuse discoloration of the skin in malaria may be due to anemia from the destruction of the erythrocytes to icterus or to hyperpigmentation. Occasionally melænum caused by large amounts of free malaria pigment in the blood serum may influence the skin color. The hyperpigmentation may compare with

⁵⁵⁰ Shapiro A. M. and Bresh A. Kala Azar in Palestine Case With Cutaneous Lesion. Tr. Roy Soc. Trop. Med. & Hyg. III 57 6° 1939.

⁵⁵¹ Acton H. W. & Napier L. E. Post Kala Azar Dermal Leishmaniasis. Indian J. M. Res. arch 15 9 106 19 7.

⁵⁵² Brahmachari U. N. A. N. = Form of Cutaneous Leishmaniasis—De mal Leishmanoid. Ind. J. M. Ga. 57 1 5-127 19 7.

⁵⁵³ Napier L. and collaborators. Post Kala Azar De mal Leishmaniasis. A series of Publications. Indian M. Gaz. 19 79 and 1930.

addisonism in intensity and distribution including oral manifestations. Racial pigmentation of the gums can be ruled out by the effect of specific treatment which however removes malarial pigment deposits but slowly. Many authors have suggested that the adrenal cortex plays a part in the formation of the cutaneous pigment in malaria and there is some pathological evidence to support the clinical facts. F. Rosenthal and Lowenthal⁴⁴ found in such a case almost complete atrophy of the adrenals. Two types of pigment occur in the skin. The



FIG. 67. Malaria tropica: malarial and butterfly-shaped pigmentation on the cheeks. Similar pigmentation has been described in filarialis, ankylostomiasis and other conditions. (Courtesy of Dr. A. Marchio in Ankara, Turkey.)

specific malarial pigment (hemozoin) is derived from the destroyed red cells. It contains iron but because of its firm grasp on the iron atom does not give the ordinary Berlin blue (Potassium ferrocyanide and FeCl) reaction. It is taken up by the reticulo-endothelial system discoloring mainly the spleen, liver and bone marrow and in extreme cases it may be found in the lumen of capillaries. The skin does not store the pigment however it may be found in blood vessels.

⁴⁴Rosenthal F. and Lowenthal R. J. Addisoniform Malaria. *Zentralblatt für Bakteriologie* 53: 534, 1931.

Hemosiderin occurs besides the malaria pigment. Skin pigmentations in malaria may also be caused by *melanin*⁵⁵. Chloasma like spots on the face are not rare. These sometimes occur⁵⁶ as the peculiar mustache shaped variety called chloasma periorale⁵⁵ which like many dermatoses of the lips leaves a thin white border



Fig. 68—Malaria tropica moribundum rash (Courtesy Prof. A. Marchionini, Ankara, Turkey)



Fig. 69—Chloasma in malaria tropica (Courtesy Prof. A. Marchionini, Ankara, Turkey)

line between it and the vermillion area. Sometimes the pigmentations in malaria are pellagroid in distribution being found over the dorsa of the hands and the knuckles.

⁵⁵ aufma H. Die pathologische Pigmentierung der Haut in der Medizin Neurologie und Psychiatrie. Handb. d. Haut u. Gk. 4. 1011. 1913.

⁵⁶ Marchionini A. Malaria Cutaneous Changes. Clinical Study. Acta Dermat. venerol. 21. 33-34. 1910.

⁵⁷ Pöschel F. V. Durch Funktionsstörungen des weiblichen Endokrinsystems hervorgerufene Hauterkrankungen. Dermat. Wchnschr. 62. 193. 1916.

addisonism in intensity and distribution including oral manifestations. Racial pigmentation of the gums can be ruled out by the effect of specific treatment which however removes malarial pigment deposits but slowly. Many authors have suggested that the adrenal cortex plays a part in the formation of the cutaneous pigment in malaria and there is some pathological evidence to support the clinical facts. F. Rosenthal and Lowenthal⁵⁴ found in such a case almost complete atrophy of the adrenals. Two types of pigment occur in the skin. The



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⁵⁴Rosenthal F. and Lowenthal H. Addison infolge Malaria Zentralbl. f. Haut u. Geschlechtskr. 21: 531, 1931.

relapses of chronic malaria in up to 30 per cent of their cases. In malaria countries it seems good advice to look for the parasites in cases of chronic and unexplained urticaria or even to try quinine as a diagnostic test.

Petechiae, purpura and other hemorrhagic symptoms have often been reported. In some of these cases⁵⁶² it could be shown that the petechiae were caused by arterial or capillary thrombi and vascular wall infiltration. *Plasmodia* could be demonstrated in the lesions. Circulatory disturbances of the hands and feet may cause painful sensations of heat as well as other paresthesias.

Gangrene of circumscribed areas with or without Raynaud like symptoms and sometimes necessitating amputation is on record in a considerable number of cases.^{561 566 567 568} It is probably caused by endarteritis. In the course of chronic malaria occasional dermatomes may occur due to the severe anemia (for example onychia⁵⁶⁹). The resistance to secondary infections is decidedly lowered. Leishmaniasis, cutaneous diphtheria and other secondary infections may take an unusual course. The most spectacular secondary infection is noma. A. Eckstein⁵⁶⁶ (in Turkey) found malaria in nineteen out of twenty two cases. The patients were mostly small boys. There is a striking parallel between the incidence of noma and the malaria mortality, in seasonal as well as in regional respects.⁵⁶⁸

Noma (Cancerum Oris, Stomatitis Gangrenosa)

Noma is a rare disease in western civilization. Eckstein⁵⁶⁶ saw only one case in ten years of service at the Dusseldorf Children's Clinic while he observed no less than forty cases during three years in the Children's Hospital at Ankara, Turkey. Similar experiences have been reported from China. Epidemics of noma were observed in former years in European hospitals. Almost exclusively a disease of childhood, noma is predominantly a nonspecific complication of acute infectious diseases. Measles, typhoid,⁵⁶⁷ congenital syphilis⁵⁶¹ and particularly malaria⁵⁶⁸ are known to create the conditions in which the peculiar gangrene of the cheek occurs. Agranulocytosis and acute leukemia are other predisposing diseases.^{569 570} Some cases without known preceding disease have occurred.

The clinical picture shows a gangrenous stomatitis which sometimes in a fulminating manner breaks through the cheek and upper lip and destroys all tissues including the bone and teeth which lie in its path. Then the well known horrible destruction of one cheek surrounding the nose results. The lesion is

⁵⁶² Fraue, L. and Faenk, I. P. Die Malariaesthanien im Klinikum und pathologisch anatom. Mitt. Arch. f. Schiffs- u. Tropenhyg. 25: 355-367 III 1.

⁵⁶³ Dor, A. E. Cutaneous Aff. due to Venous Dist. Brit. J. Dermat. 15: 418 1908.

⁵⁶⁴ Leo, F. Gangr. of Feet in Adult Larvate Periodic Malaria. Arch. Ital. d'Chir. 1045 1051 1935.

⁵⁶⁵ Eckstein, A. Stomatitis Gangrenosa. Am. J. Dis. Child. 59: 219-237 1940.

⁵⁶⁶ Lohr, A. J. and Rose, D. E. A Case of Cancerum Oris Following Typhoid Fever With Plastic Repair. Can. M. A. J. 25: 416-449 1931.

⁵⁶⁷ Hantz, W. Noma. Hb. 1937. Dissert. n.

⁵⁶⁸ Hantz, W. Zur Krankheitsauffassung der Noma und gliedertartig. Fortsch. d. Gewebebrandes. Zentralbl. f. Chir. 1854 1863 1934.

⁵⁶⁹ Hantz, W. Infectious Gangrene of the Skin Due to Bacterial Synergism. Arch. Surg. 31: 253 1935.

decidedly unilateral causes little or no pain and temperature and even appetite are much closer to normal than one would expect a surprising observation which can also be made in the final stages of destructive oral cancers

There is no strong leukocytic reaction¹⁶⁶. Only in the late stages does general toxemia develop. The post mortem examination reveals necrotic and degenerative liver and spleen changes. The mortality is based on 173 cases from the literature is 95 per cent. Eckstein¹⁶⁶ after switching from neoarsphenamine which proved disappointing to antgangrene serum in large doses locally intra muscularly and intravenously had more than 50 per cent recoveries in twenty one cases

Although there is no complete agreement about the cause it is assumed by most authors that Plaut Vincent's symbiosis of fusiform bacilli and spirillae plays an important part. These microorganisms have frequently though not always¹⁷¹ been found in the lesion and in the surrounding apparently normal tissues¹⁶⁸

Amebiasis Cutis

Ulcerations of the skin caused by *Endamoeba histolytica* occur in amebiasis either in connection with an operative abdominal wound or around the anus or without direct connection with the infected viscera for example on the glans penis. The amebic ulcers¹⁷² are rapidly spreading lesions. Varying activity in different portions of the margin causes an irregular jagged outline. The edge is undermined purulent and surrounded by a red halo. The floor is covered with indolent granulations and pus. The skin lesions respond to emetine

¹⁶⁶Friedmann J. L. ■ Noma der Wangen Schweiz med Wchnschr 1930 I 61 63

¹⁷²Engman A. F. J. and Metteney H. E. Amebiasis Cutis (Etiology histology) Arch Dermat & Syph III 1 1 1931

CHAPTER VII

SYSTEMIC INFECTIONS

Rickettsial Diseases

Rickettsial diseases of man and many animals are caused by gram-negative, coccoid or bacillary intracellular microorganisms which are usually borne by arthropods especially lice and ticks and which need tissue containing media for successful culture. With the exception of the rickettsiae of the otherwise different Q fever they are not filtrable.⁵² The serum of patients with rickettsial diseases agglutinates specifically certain strains of *Bacillus proteus* (Weil-Felix reaction). The clinical appearance of the rickettsioses of the typhus group is best illustrated by its most important representative typhus itself from which the others differ but little.

TYPHUS FEVER

Typhus fever (typhus exanthematicus) is a severe endemic and epidemic disease the importance of which for the human race equals that of plague and cholera.⁵³ It has accompanied most of the wars and famines and other upheavals of history. Its victims in Ireland during the early decades of the nineteenth century numbered millions. The epidemic form is possibly with a few exceptions spread by body lice. After an incubation period of thirteen to fourteen days the patient suddenly develops fever, chills, severe headaches, and prostration. The fever is continuous, ending by rapid lysis after approximately two weeks. Temporary mental disturbances during the fever and insomnia are common. The attack is followed by a long period of convalescence which may last two or three months. The attack is characterized by a rash, stupor, low blood pressure, tender and enlarged spleen (denied by Gordon⁵⁴) and various gastrointestinal and renal symptoms. The loss of weight is very marked.⁵⁵ The blood shows a shift to the left and thrombocytopenia which may reach 100,000 during the fifth to eleventh days.⁵⁷ The mortality rates vary widely. Children and groups who have been exposed for a long time to infestation with lice are often only mildly ill. In people beyond 50 years of age, in the undernourished, and in newcomers from disease-free countries who are not accustomed to body lice, for example physicians and nurses, the disease is apt to take a more severe course with mortality rates higher than 50 per cent.

⁵²Dyer R. F. Typhus Rickettsial Diseases. JAMA 124: 1165, 1944.

⁵³Zins H. Ras Liess d. History. New York 193. Little Brown & Company.

⁵⁴Codon D. M. Brit. Med. J. 39: 653-655, 1910.

⁵⁵Virus of Rickettsial Diseases. H. and University Press, Cambridge, 1910. article by J. E. Codon pp. 1-571.

⁵⁷Schittgen H. A. Da. Fleckfieber Haefeld. Intern. Med. 19: 645-68, 1910.

The gross pathology is unrevealing but the severity of the systemic infection is shown by typical widespread microscopic vascular lesions in the central nervous system the heart and especially the skin



Fig 7 Typhus lesion on the second day of exanthem showing the both lateral cells and well defined perivascular cellular reaction (Courtesy Woodward Th B and Han F F J A M A)

The infection conveys lasting immunity

The diagnosis is based on the clinical picture the epidemiologic conditions and the Weil Felix reaction Sometimes complement fixation tests and biopsy of a skin lesion are useful

Dermadromes—The importance of the rash is reflected in the various names of the disease such as spotted fever typhus exanthematicus Fleckfieber fièvre exanthématique Murchison (after Curschmann⁴⁷⁰) collected nineteen different terms referring to the rash

In the first two days of the fever an *initial exanthem* consisting of a few 1/2 mm wide petechial papules on the trunk can sometimes be observed⁴⁷¹ The initial exanthem may occasionally be morbilliform or urticarial⁴⁷²

⁴⁷⁰Curschmann H Das Fleckfieber Neoth agei Special Pathology u i Th aplc Vol III Wien 1900 Alfred Hölder

⁴⁷¹Lipschütz H Die histik des Fleckfieber exanthem Arch f Bakt u Hyph 126 414 537 1919

The main rash appears most often on the fourth to sixth day of the fever rarely as early as the second or as late as the ninth day⁵⁸⁰ The eruption is often preceded by a characteristic drop in temperature In the early stages before it becomes plainly visible the rash can be demonstrated by a warm bath or a tourniquet⁵⁸¹ The most comprehensive dermatological evaluation of the rash has been given by Lipschutz⁵⁷⁹ This article contains excellent illustrations

The rash appears continuously and not in a series of crops so that the definite number of spots is reached within one or two days⁵⁸² The eruption begins on the upper abdomen and chest then in rapid succession spreads to the back and to the extremities The armpits and the inner surfaces of the upper arms are the places to look first for spots⁵⁸³ The fully developed rash may be extremely copious with the greatest density on the trunk From the trunk to the arms and to the face the density decreases on the whole with some accentuation on the dorsa pedum which is in contrast to the scarcity of lesions on the thighs and lower legs Eruption on the palms and soles is not the rule The exanthem starts with pale ill-defined pinhead to lentil sized hardly palpable often irregular maculae which as soon as they have reached a few millimeters in size no longer fade completely under glass pressure Confluence of neighboring lesions into irregular and slightly raised spots occurs The color is not bright red but has an increasingly brownish tinge This indicates the hemorrhagic component which manifests itself in more or less numerous petechiae within and between the spots The purpuric phenomena are a measure of the severity of the infection⁵⁸⁴ Purpuric lesions are often found in the folds and on the back In the mature stage which is reached around the twelfth day the color is decidedly purplish and a delicately bluish marbled vascular pattern may be seen between the lesions which is easier to recognize from a short distance in moderately bright light The old physicians called this subcuticular mottling or mulberry rash (Buchanan and W Jenner after Baumker and Aschoff⁵⁸⁵) After the twelfth day the exanthem fades leaving yellowish brown pigmentation which may persist for a while A slight branny desquamation which can be provoked by gentle rubbing takes place during and some days after the fading⁵⁸⁶

In up to 20 per cent of the cases varying with the epidemics no exanthem could be observed A macular erythema is occasionally seen on the buccal mucosa It precedes the exanthem Initial conjunctivitis is common Herpes is rare The nails often register the severe disease by a white transverse line (Botkin and Pietnew after Schittenhelm⁵⁷⁷) Pietnew⁵⁸⁰ saw longitudinal fluted lines

The micropathology of the lesions has been studied by F Frenkel⁵⁸⁷ and Baumker and Aschoff⁵⁸⁸ There are foci of hyaline degeneration necrosis and

- ⁵⁸⁰Pietnew W D Flecktyfus Moskau Föld ml 1917 19 9 Ztschr f klin Med 83 24-301
⁵⁸¹Pusch J Dtsch med Wochenschr 1917 43 1111-1112
⁵⁸²Oyer R P Typhus M CH North Am J 27 7 5-759 1943
⁵⁸³Baumker C A Aschoff F Fleckfieber Med Klin 11 95-99 1915
⁵⁸⁴Defama C L et al ur la lequamation sur ra se dans le typhus exanthématique Bull Acad d m d 86 306 30 1911
⁵⁸⁵Fra nk I F Zu pathologisch Anatomi des Fleckfiebers München med Wchnschr 63 969 971 1921

endothelial proliferation in the intima of the small arteries and precapillaries. These lesions form protruding intravascular buds and may give rise to small thrombi. In the endothelial cells rickettsias have been found in small numbers.⁵⁸⁶ Furthermore, there is a perivascular infiltration of lymphocytes, plasma cells and epithelioid cells which resemble adventitial histiocytes. These changes are found in the papillary vessels of the skin and especially throughout the brain and heart.

No specific treatment is known. A prophylactic vaccine is available.

A mild variety of typhus known as Brill's⁵⁸⁷ discrete endemic or murine typhus with a mortality rate of less than 4 per cent is endemic in the east and southeast of the United States and in many ocean harbors. The disease is harbored by rats and transmitted by rat fleas and rat lice.⁵⁸⁸ The exanthem was seen in 64 per cent of 115 cases,⁵⁸⁹ appearing about the fifth day, starting on the trunk and spreading centrifugally, rarely reaching the face and palms. There often were only a few maculopapular lesions of 2 to 5 mm in diameter.

ROCKY MOUNTAIN SPOTTED FEVER

Much more dangerous than endemic typhus is Rocky Mountain spotted fever. Approximately 600 cases occur every year in the west and 200 additional cases in the remainder of the United States. The average mortality is 12½ per cent. This rickettsiosis is caused by *Rickettsia rickettsii* and transmitted by various ticks.⁵⁸⁹ The clinical picture resembles typhus closely. A mottled initial rash has often been seen to appear with the fever, thus preceding the exanthem,⁵⁹⁰ which breaks out between the second and sixth days of the illness. It is rarely seen below the elbows and knees or on the face.⁵⁹¹

The rather copious rash is like the typhus eruption at first maculopapular and red, especially in the evening. Later it is petechial and even frankly purpuric, especially in severe cases. The rash is followed by desquamation and pigmentation. The individual lesion measures 2 to 4 mm in diameter.⁵⁹² The rash may be extremely profuse⁵⁹³ with hardly any normal skin left or it may be very sparse and even completely absent. It may appear in successive crops.⁵⁹⁴ Hemorrhagic factors may cause the usually discrete lesions to coalesce into purpuric areas which may involve the entire body. Congestion of the soft areas like the scrotum or the soft palate may occur.⁵⁹⁵⁻⁵⁹⁷ In thundering eruptions the skin is very tender. The distribution is a little different from typhus in that the rash most often⁵⁹⁸ appears first on the flexor surfaces of the wrists⁵⁹⁹ and ankles.

⁵⁸⁶Wickl H. Rickettsia in Exanthematico et in hemorrhagico. *Ann. Intern. Med.* 1934; 1: 1-17.

⁵⁸⁷Brill N F. A discrete febrile illness of unknown origin. *Am. J. Med. Sc.* 129: 181, 1910.

⁵⁸⁸Quart D M. A fatal case of murine typhus. *Ann. Int. Med.* 23: 10, 1934.

⁵⁸⁹Clark R R. Rocky Mountain spotted fever. *J. A. M. A.* 116: 1, 3, 1934.

⁵⁹⁰Anderson L. Spotted fever. *Illnesses* 2: 830-813, 1913.

⁵⁹¹Toppling N H. Rocky Mountain spotted fever. *Med. Clin. North Am.* 27: 722-733, 1913.

⁵⁹²Floyd M L. Rocky Mountain spotted fever. *J. Iowa Med. Soc.* 27: 791, 1937.

⁵⁹³Raker C F. Rocky Mountain spotted fever. *W. Va. Med. J. & Surg. Journal* 1913; 13: 1913.

⁵⁹⁴Clark R R. Rocky Mountain spotted fever. *Ann. Int. Med.* 17: 17, 1914.

⁵⁹⁵Ong H A and Raffetto J F. Rocky Mountain spotted fever. *J. Pediatr.* 17: 617, 1930.



Fig. 73. Rocky Mountain spotted fever. Patient complicated by exfoliative dermatitis. Noting the thickened skin in the skin of the neck and arms. (Courtesy Dr. F. H. Haskin.)

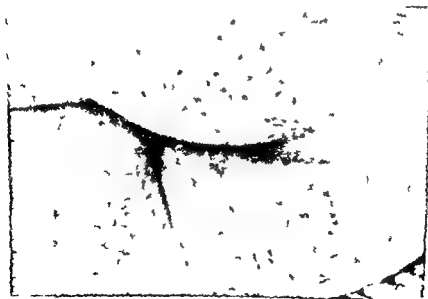


Fig. 74. Rocky Mountain spotted fever. (Courtesy Dr. R. R. Baker, U.S. Public Health Service, Rocky Mountain Laboratory.)

spreading centripetally from there within two days ⁵⁹³ to the back the arms the legs and the chest and finally to the abdomen, where it is least pronounced. Palms soles and face are involved last ⁵⁷². There is some relief of the muscular aches and pains after complete eruption.

Fig 75

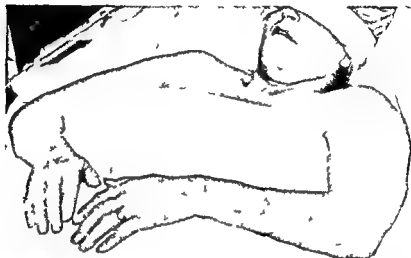


Fig 76

Fig 75 —Rocky Mountain spotted fever. Rash in typical centripetal distribution. Arm (Courtesy Dr. E. Baker)

Fig 76 —Rocky Mountain spotted fever. Not great density toward the foot = 1 purpuric spots on the thigh. Arm (Courtesy Dr. G. F. Baker)



Fig 77 —Rocky Mountain spotted fever : Dense rash on the hands (Courtesy Dr G E Baker)

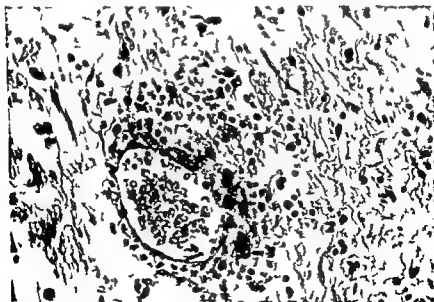


Fig 78 Rocky Mountain spotted fever : Lin blood on thirteenth day. C.R. 8x ill g of endothelial cell perivascular exudate. From D. R. E. Lill (Pathology of Rocky Mountain Spotted Fever U. S. Public Health Service)

No specific treatment has become recognized except hyperimmune rabbit serum which is useful only during the first days. Early removal of the tick may prevent infection. A specific vaccine from egg yolk culture is of prophylactic value.⁵⁷³

FIEVRE BOUTONNEUSE MARSEILLES FEVER OR FIEVRE ÉRYTHÉMATIQUE ESCARRO NODULAIRE

Fievre boutonneuse, Marseilles fever or fièvre érythémateuse escarro nodulaire is a rickettsiosis of the Mediterranean areas. It is transmitted by a tick which feeds on dogs carrying the causative organism *Rickettsia conorii*. The course resembles mild typhus, the mortality rate being less than 3 per cent. The rash is more papular than in typhus⁵⁹⁶ and later often purpuric. Cases without eruption occur.⁵⁹⁷ The rash starts on the trunk, legs and arms and involves the face last. The palms and soles are commonly involved, the abdomen staying relatively free. At the onset the tick bite is frequently visible as a lentil sized shallow ulcer with a black necrotic center. This lesion is called tache noire.⁵⁹⁸ It is of diagnostic importance but not always recognizable.

TSUTSUGAMUSHI DISEASE JAPANESE RIVER FEVER OR SCRUB TYPHUS

Tsutsugamushi disease, Japanese river fever or scrub typhus is a rickettsial disease of the west Pacific area. It is endemic in flooded areas and along rivers. The cause *Rickettsia orientalis* is transmitted by a mite which infests rodents especially rats and a field vole.⁵⁹⁹ According to Dyer⁵⁷³ the disease takes a typical typhus course of about seventeen days' duration. The infecting bite causes a necrotic or scrub covered ulcer in about 75 per cent of the cases. The primary lesion is 2 to 10 mm in diameter with an indurated red areola and is accompanied by a smooth tender nonsuppurative lymphadenitis which only rarely extends beyond the portal area.⁶⁰⁰ The initial eschar is of diagnostic value. The rash which appears on the fourth day is noticeable only in about one half of the cases⁶⁰⁰ and is often preceded by a dusky flush on the face and neck.⁵⁹⁷ It resembles that of spotted fever although Dyer⁵⁷³ emphasizes the lack of hemorrhagic tendency. Characteristic eye ground changes and generalized peripheral lymphadenopathy are almost constant findings. The disease was known to have a fatality rate of 15 per cent, but in a recent series of sixty-four cases only 1.5 per cent of the patients died.⁶⁰⁰ No specific therapy and no vaccine have been developed.

⁵⁷³Boiret J. J. and Dunan. Recherches nouvelles sur la fièvre érythémateuse du littoral méditerranéen. Bull. An. de méd. Paris 100: 915-960, 1934.

⁵⁷⁴Raynaud A. Tache noire et fièvre érythémateuse. Bull. Soc. path. exot. 30: 6, 7, 1937.

⁵⁷⁵Blak F. C., Ma J. I. F., Sado K. J. F., Jr., Kobayashi G. M. and H. H. F. J. Tsutsugamushi Disease: Typhus Mite-Borne Typhus. In New Guinea Epidemiology (Clinical Observations and Etiology). Am. J. Hyg. 41: 43, 1941.

⁵⁷⁶Alm C. F. and Lipschutz J. Tsutsugamushi fever in the Southwest Pacific Theater. J. A. M. A. 121: 109-1100, 1941.

⁵⁷⁷MacCalla T. F. and Forrester J. A. Tsutsugamushi Disease. Am. J. Med. Sci. 210: 38, 1941.

TRENCH FEVER OR WOLHYNIA FEVER

Trench fever or Wolhynia fever a benign recurrent fever common among soldiers of World War I is caused by a rickettsia found in the epithelial cells of the stomach of the body louse⁶⁰¹ The observations on the frequency of macular micropapular scarlatiniform or petechial rashes and of erythematous enanthems vary widely^{673 601 60}

Carrion's Disease (Bartonellosis) Verruga Peruviana

In 1885 Daniel Carrion a Peruvian medical student inoculated himself with blood and tissue from a lesion of verruga peruviana an eruptive disease occurring in certain South American valleys mainly in Peru He died five weeks later of Oroya fever a clinically very different syndrome This experiment strongly suggested the etiological identity of the two diseases which after much controversy has become generally accepted The cause of both forms which may occur independently simultaneously or successively⁶⁰³ is Bartonella bacilliformis a minute rod shaped parasite of the red blood cells Culture (Battistini after Fox⁶⁰⁴) and animal inoculation⁶⁰⁵ have been successful^{604 606} The infection is transmitted by the sandfly *Phlebotomus verrucarum* the habitat of which corresponds to the few areas of endemic Carrion's disease Fifteen to forty days after the infection the patient comes down with irregular fever malaise and anemia If the disease takes the course of Oroya fever which has a mortality of 40 per cent the onset is sudden and the fever is at first continuous later remittant The main feature is an acute severe anemia with a blood picture which resembles that of pernicious anemia The red count may fall as low as 500 000 In addition there is a leukocytosis of about 20 000 Fox⁶⁰⁴ remarks that there is probably no condition except hemorrhage which can cause severe anemia so quickly The erythrocytes contain bartonellas in great numbers Skin lesions are scanty They are more numerous in the benign form called *verruca peruiana* which has the same incubation period but in which the fever and anemia are less severe

The Spanish word verruga is used for all types of cutaneous excrescences and it should not be taken as a synonym for the dermatological term verruca The characteristic lesions of the disease are nodules or tuberous masses which vary from pinhead to apple size and from a few usually large lesions to innumerable small efflorescences One therefore speaks of miliary and nodular forms although there are many transitions The rash comes on in crops and is itchy especially when it heals The duration of the cutaneous form is variable on

⁶⁰¹ Ju gmann P Das wolhynisch Fieber Berlin 1919 Julius Springer

⁶⁰² Schitt nh im A Wolhynisch s Fieber ol Fünftag H r Halbb J Jan Med in Vol I Berlin 1925 Julius Springer

⁶⁰³ Me H Pres at Statu f Human Barton Host Bol Off san panam H 301-309 1943 Ab tr Trop Dis Bull 40 904 1943

Fox H Verruga i uana—F rsonal Experiment I Tru J A M A 106 93 931 1935

Jadassohn J an l e fte t t r in n Fall von Verruga peruiana C be trachtung auf Aff Ztschr f Hyg u l fecti skrankh H 4 1910

⁶⁰⁴ D Rocha Lima H Verruga peruiana oder Carrionsch Krankh it (Oroya fieber) Handb d H u Gk H l 1 135 1 1937

the average from four to six months (Odriozola⁶⁰⁷) The military verrugas appear quite symmetrically on the extensor surfaces of the limbs on the ulnar aspects of the hands and forearms⁶⁰⁷ and on the face The body the palms and soles and the genitalia usually remain free⁶⁰⁴ The individual lesion starts as a flat red hemorrhagic papule There are subcutaneous and cutaneous lesions the depth explaining the variations in color The nodule grows so that at first a sessile and later a pedunculated bluish red conical or hemispherical tumor on a base of ringlike pigmented folds results The lesions are firm at first but soften later Small lesions look like senile hemangiomas⁶⁰⁴ The verrugas bleed easily If the verruga is at its height the surface is glossy a little moist and the color cherry red much like a fresh hemangioma or granuloma telangiectaticum The verruga has a marked spontaneous healing tendency It may shrink or drop by atrophy of the base Bleeding is common and secondary infection occurs Lesions in the mouth the nose and the conjunctivae have often been observed They have been found in the entire length of the gastrointestinal tract and on the serous membranes These lesions may cause serious hemorrhages⁶⁰⁷

Very large intracutaneous and subcutaneous sarcoid infiltrations of irregular shape may develop probably by coalescence of nodules Large ulcerated granulomas are called mulas because the Peruvians believe that these big forms stem from infected mules Infantile cases are usually mild

The histological picture shows a sharply bordered vascular granuloma which consists mainly of endothelial cells (verruca cells) and inflammatory infiltration There are many variations some suggesting sarcoma angioma or myxoma⁶⁰⁴

Dr Rocha Lima⁶⁰⁸ and other authors found in the protoplasm of the verruga cells inclusion bodies which were considered to be an adaptation of the bartonellas to intracellular life

The diagnosis rests on the unique dermatological aspect the history of a stay in a verruga area the fever and blood picture agglutination⁶⁰³ and finally on the biopsy Leprosy and yaws must be ruled out

⁶⁰⁷Odriozola J La maladie de Carrion ou la verruga Peruvienne Paris 1909 Carré & Naud

⁶⁰⁸How C Carrion's Disease Arch Int Med 72 147 1913

CHAPTER VIII

SYSTEMIC INFECTIONS

Mycoses

Fungus infections are among the most common skin diseases but systemic mycotic infections are rare if one does not count the trichophytids

COCCIDIOIDOMYCOSIS

The name coccidioidomycosis is preferable to coccidioidosis a term which may easily be confused with the protozoonosis coccidiosis. The disease is endemic in dry dusty areas of some western states⁶⁰ especially the San Joaquin Valley in Southern California^{61 62} where from December, 1937 to May 1939 432 acute infections of San Joaquin Fever were registered. There is a peak of incidence in the fall. It is to the great merit of Dickson⁶³ to have shown that the acute respiratory infection known as San Joaquin Valley fever is the primary stage of coccidioidomycosis. The danger of such an endemic focus is illustrated by the fact that during recent military maneuvers in one of the endemic areas probably far more than the known seventy five cases occurred among several thousand soldiers.⁶⁴

The cause is the fungus *Coccidioides immitis* which has a saprophytic hyphae phase and parasitic spherules or cysts which are double contoured refractile bodies which break up into radially arranged segments (endospores). In the infected person or animal these spores develop new spherules. The infection is mainly air borne and but rarely occurs through the skin. The acute disease does not seem to be contagious from man to man as shown by the failure to infect even a bedfellow.

The air borne parasite causes a *primary lung infection* which probably often remains asymptomatic but may manifest itself by severe chest pain, irritating cough, severe headache, prostration and fever. The whole syndrome resembles influenza or pneumonia.⁶⁵ In rare instances a primary lesion is found in the skin.⁶⁶ A transient macular initial rash has been observed in some patients.

⁶⁰Smith C E. Epidemiology of Coccidioidomycosis With Erythema Nodosum. Am J Pub Hlth 30 600-611 1940

⁶¹Dickson E G. Primary Coccidioidomycosis: the Initial Acute Infection Which Results in Coccidioides Granuloma. Am Rev Tuberc 38 711-7 1935

⁶²Smith C E. Coccidioidomycosis. M Clin North America 27 790-807 1943

⁶³Goldstein B M and Louis G. Primary Pulmonary Coccidioidomycosis. War Med 4 299-317 1943

Winn W A and Johnson G H. Primary Coccidioidomycosis—Etiogenographic Study of Forty Cases. Ann Int Med 17 407-427 1943

⁶⁴Kessel J E. Coccidioidomycosis. Am J Trop Med 21 447-453 1941



Fig. 5—Ecthyma gangrenosum like rash in patient with *Histoplasma* (San Joaquin River) (Courtesy Dr. E. Smith)



Fig. 60—*Histoplasma* of scrofulous type like lesion about the neck (Courtesy Dr. H. P. Johnson)

Within the first three weeks of the acute respiratory phase erythema nodosum of typical distribution along the shins about the knees and on the lateral surfaces of the thighs or erythema multiforme on the arms and occasionally on the face may break out. Goldstein and Louie⁶¹ found an incidence of 25 per cent among infected soldiers all of whom probably were newcomers in the area but other percentages are much lower about 4 per cent.⁶¹⁵ Occasionally a morbilliform eruption has been noticed.^{611 616 617 618} Severe arthritic pains sometimes with swelling of the joints⁶¹⁹ have given rise to the term deert rheumatism. Conjunctivitis is sometimes a feature of this stage. Erythema nodosum is a frequent finding. Smith⁶¹ stresses the appearance of erythema nodosum at the time the coccidioidin test becomes positive.

The prognosis of the primary acute febrile phase is good the mortality being less than 1 per cent. After recovering from an attack of San Joaquin fever the patient usually remains in good health without further attacks. The coccidioidin test remains positive for a long time.

The diagnosis of primary coccidioidomycosis is hardly made from the clinical picture alone although tuberculosis like *Y. rav* changes in the lungs⁶¹² with negative bacillary and allergic findings may suggest it. The history of having lived in an endemic area the finding of spherules in the sputum and a positive coccidioidin skin test secure the diagnosis. The cutaneous reaction becomes positive two to seventeen days after the onset of symptoms. In about 1 out of 1000 cases a progressive secondary granulomatosis develops which is fatal in more than 50 per cent and may predominantly involve the respiratory tract the bones the central nervous system and least often the skin. Coexistence of lung foci in cases which clinically seemed to be restricted to the skin has been demonstrated at post mortem.⁶²⁰ Several clinical varieties of a severe dermatosis have been described. Jacobson⁶¹ classifies the lesions into those of cutaneous subcutaneous and lymphadenitic origin. The skin nodules which in their further development may invade the subcutis are mainly found on the face about the neck and on the distal parts of the extremities. The nodules are painless deep seated and pink to dusky red. They occur in various sizes and shapes and finally ulcerate and exude a grayish yellow pus containing *Coccidioides immitis*. From these dermic lesions fungating papillomatous granulomas may arise creating a picture resembling mycosis fungoides. Widespread cutaneous lesions may heal with atrophic scars. Chronic sarcoid and lupus vulgaris like pictures have been observed.⁶

⁶¹Willitt F M and Weiss A. Coccidioidomycosis. In Southern California. Report of New Endemic Areas With Review of 100 Cases. Ann Int Med 23: 349 1945.

⁶¹²Gottlieb D M and McDonald J B. Primary Pulmonary Coccidioidomycosis. J Clin Invest 121: 557 561 1944.

⁶¹³Fabry H K Smith C E and Dickson E C. Acute Coccidioidomycosis With Erythema Nodosum in Children. (San Joaquin Fever). J Pediatr 15: 163 171 1939.

⁶¹⁴Dickson E G. Coccidioides Infection. Ann Int Med 59: 109 1937.

⁶¹⁵Rosenberg E H Dockerty M B and Myrdal H W. Coccidioidomycosis Affected by Sulfanilamide and Nitroglycerin. Arch Int Med 59: 224 90 1942.

⁶¹⁶Eptel E. Prognostic Significance of Cutaneous Lesions in Coccidioidomycosis. Arch Dermat & Syph 38: 75 75 1934.

⁶¹⁷Jacobson H B. Immunotherapy for Coccidioidomycosis. Arch Dermat & Syph 40: 521 540 1939.

⁶¹⁸Zelinger F I. Chronic Coccidioidomycosis. Arch Dermat & Syph 25: 5 71 1937.

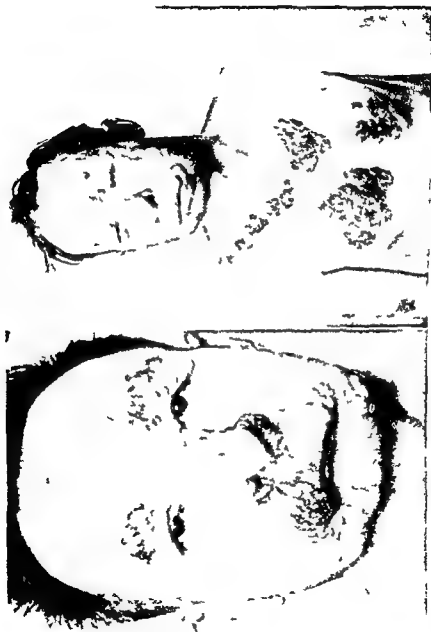


Fig 81

Fig 82

Fig 81 —Coccidioid dermatitis verrucous papules (From Ziler E P Arch Dermat 1932)

Fig 8 —Chronic coccidioid dermatitis later stages verrucous papules (From Ziler E P Arch Dermat 1932)

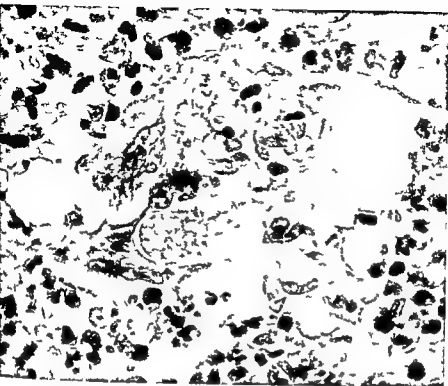


Fig. 84

Fig. 83 — Chronic coccidioid dermatitis. Crusted areas, nodules and annular pigmented scars. (From Zeller F. I. Arch. Dermat. 1032.)
 Fig. 84 — Coccidioidomycosis. Granuloma with glaucous material containing a sporulating cyst with capsule ruptured at one end. (From Zeller F. I. Arch. Dermat. 1032.)



Fig. 83

The appearance of acute military pedunculated or sessile dermic granulomas usually on the face is of ominous significance⁶⁰. Their appearance is often preceded by symptoms of pulmonary or meningeal involvement. Such patients usually succumb to the coccidioidal infection in from six to twelve weeks after the appearance of the eruption. In some of these cases the fungus could be grown from the blood.

The course of the subcutaneous and lymphadenitic lesions is more chronic and relatively more benign. The subcutaneous granulomas are frequently the first cutaneous manifestations⁶¹. They start as soft frequently tender masses anywhere on the body and may form large flaccid tumors, cold abscesses and sinuses. If the flaccid tumor or abscess is surrounded by an extensive inflammatory infiltrate a hard gummatous lesion results. Finally just as in tuberculosis to which many clinical parallels exist specifically involved superficial lymphatic nodes may especially in the submyiliary region create scrophuloderma like lesions with abscesses, sinuses and scars.

The histopathology of the coccidioidal lesions is that of an inflammatory granuloma with marked tuberculoid tendencies. There is edema and a diffuse cellular infiltrate predominantly composed of lymphocytes epithelioid and giant cells of the Langhans type. These giant cells harbour the coccidioidal spheres which have been demonstrated in the process of rupturing and releasing the spores^{61,6}.

The treatment is still unsatisfactory. Jacobson⁶¹ who has had wide experience with coccidioidomycosis reviewed in 1939 the many methods of treatment. Intravenous injections of a 1 per cent solution of antimony and potassium tartrate⁶², intramuscular injection of colloidal copper, oral administration of potassium iodide, arsenic or combinations of these agents and roentgen therapy have not given convincing results. Jacobson⁶¹ now feels that immunizing therapy is superior to the chemotherapy known so far and has had 20 per cent good results (personal communication). The patients are in intervals of one to two weeks given intravenous injections of vaccine starting with 0.05 cc. and increasing by 0.05 cc. each time. A course consists of twelve injections. Between the courses is a rest period of six to eight weeks⁶³.

TORULOSIS

Only a few cases of systemic infection with the yeastlike fungus *Torula histolytica* (*Debaryomyces neoformans*) are known. Tuberculosis resembling granulomas in the brain, the lungs, the gastrointestinal tract and other organs is the outstanding feature of the disease. The comprehensive monograph of

⁶⁰ Evans, N. and Hall, H. A. Coccidioidal granuloma—J. Clin. J. N. A. 93: 1891-1903.

⁶¹ Guy, W. H. and J. A. of F. M. Granuloma Coccidioides Ar. II. Dermat. & Syph. III: 308-19.

⁶² Stewart, R. A. and Kimura, F. Skin Test for Coccidioidal Infection. J. Infect. Dis. 66: 21-217, 1940.

Stoddard and Cutler⁶⁵ emphasized the lack of skin manifestations. Since then a few cases with dermatomes have been reported.^{67, 68}

Acneiform pustules, granulomatous ulcers and deep seated abscesses, nodules or plaques⁶⁹ varying from almond to hand size without ulcerative tendency have been observed. The histopathologic characteristics of cutaneous torulosis include tuberculoid granulomas with caseation and enormous numbers of giant cells containing the double contoured oblong or spheroid refractile organisms. There exists a close similarity between torulosis and coccidioidomycosis.⁶⁷

BLASTOMYCOSIS

H. Montgomery⁶²¹ complains about the loose use of the term blastomycosis. He suggests that the word should be used only for the disease described by Gilchrist⁶²² in 1896 and not for all infections caused by yeastlike organisms.

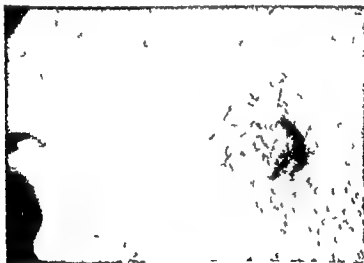


Fig. 35.—Blastomycosis. Primary lesion of the extremity in a tuberculoid verrucosa.

The American blastomycosis is caused by the yeastlike fungus *Monilia dermatitidis* which can be demonstrated in the pus or in the tissues as a refractile double contoured budding round organism often appearing in unequal pairs.

- ⁶⁵Stoddard J. I. and Cutler F. C. Torula Infection in Man. Monograph 6. New York 1916.
 Rockwell Institute for Medical Research.
⁶⁷Urbach F. and Zahnd H. Die Blastomycose (torulose). Arch f. Dermat. Syph. 182: 401-411 1930.
⁶⁸R. ppaport H. Z. and Kaplan H. Generalized Torula Mycosis. Arch. Path. 2: 10 1936.
⁶⁹Wellman F. D. Cutaneous Torulosis. South M. J. 28: 851-853 1933.
⁶²¹Will C. J. Cutaneous Torulosis. Arch. Dermat. & Syph. 31: 54-66 1925.
⁶²²Montgomery H. Blastomycosis. M. Clin. North America 22: 651-662 1930.
 Gilchrist T. C. Blastomycosis. Derm. Clin. Johns Hopkins Hosp. Rep. 1: 269 1896.

PLATE I

- 1 Acute septicemia Bullous rash with hemorrhagic component Fatal outcome
- 2 Acute septicemia Purpuric bullous rash
- 3 Lupus vulgaris planus Note brownish spots under glass pressure
- 4 Tubercular ulcer of the tongue in pulmonary tuberculosis (Case of Dr. J. V. Cookman)
- 5 Systemic blastomycosis Progressive skin lesion
- 6 Systemic blastomycosis Progressive and stable lesions



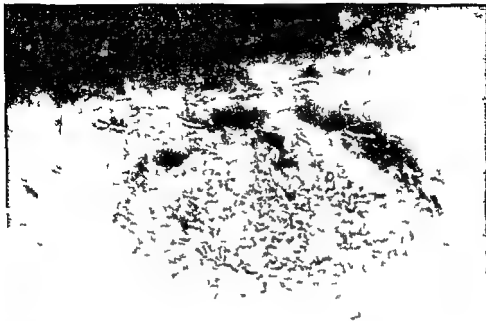


Fig 86 — Blastomycosis. Leg lesion. Not bulging edge with small abscess. In the pus of the abscess one is likely to find the yeast.



Fig 87 — Blastomycosis. Small lesion in yeast infection.

The organism grows well on the usual fungus media where it develops mycelia which are not found in the lesions.

Blastomycosis may occur as a primary skin infection and in the majority of the cases it remains a dermatosis. A fraction of the skin cases may become systemic and involve other organs setting up internal foci which may metastasize and thus secondarily involve the skin.⁴² The widely scattered subcutaneous rather indolent nodules may develop slowly into cold abscesses which may reach large size. The even and symmetric distribution of nodules and abscesses and their frequent involvement of the covered parts in contrast to the ectogenous lesions which favor the face, arms and hands indicate their hematogenous pathogenesis. The abscesses may form ulcers and sinuses from which typical blastomycotic skin lesions may arise.



Fig. 84 — Blastomycosis. Gumma like hematogenous lesion.

The primary skin lesion of blastomycosis is a papulopustule which slowly grows peripherally. Within a few months it forms⁴³ a coin shaped thick firm elevated patch the surface of which is papillary or verrucous and often fissured or lobulated. The center becomes depressed as soon as the lesion has reached the size of about a half dollar. The most characteristic feature is the steeply raised succulent red border in which many pin point to pinhead sized abscesses are contained. By means of pressure and a magnifying glass they can easily be made visible. The small quantity of pus which can be expressed from the tiny abscesses is the best material for microscopic study and culture. The lesions may by growth and coalescence attain large size and even cover entire regions. The center of such large lesions is often scarred but there are active foci scattered throughout the scar tissue in varying density. The active foci in old lesions are often crusty, oozing with serum and pus and apt to bleed on the slightest touch. The destructive power of such large blastomycotic granulomas

⁴²Ormsby H. S. and Montgomery H. J. *Diseases of the Skin Philadelphia 1943 Lea & Febiger*

■ great. Prominent soft parts for example the scrotum⁶³ the alae nasi and the lids may suffer great damage. The polycyclic border of old lesions remains more or less papillary often cordlike. The scarring does not always keep pace with the extension of the lesions so that large areas may remain thickly covered with red beds of vegetating masses. In other cases the peripherally progressing border leaves in its wake a smooth red ulcerative area almost devoid of any healing tendency.



Fig. 49. Unusually extensive blastomycosis. This type of blastomycosis lesion resembles tuberculous ulcers. This case healed after two months of treatment with iodine and x-ray. (From Bush J. B. Arch Dermat. 1941.)

In 50 per cent of the systemic cases the first symptoms are referable to the respiratory tract. The picture may resemble that of a cold or of an attack of influenza. In 4 per cent the primary lesion followed an injury; in 19 per cent a skin lesion was noted first and in 23 per cent the earliest lesion was a subcutaneous nodule or abscess often on unexposed parts⁶⁴. Besides a great variety

⁶³ Martin D. S. and Smith D. T. Blastomycosis. Review of Literature. *Am. Rev. Tuberc.* 39: 275-304, 495-515, 1939.

of occasional organic involvements the bones mostly the vertebrae and joints become infected in about 50 per cent of the systemic cases

The histopathology reveals a granuloma with varying mixtures of leukocytes lymphocytes plasma cells and Langhans type giant cells which often contain some fungus elements. Tubercle formation is not marked

Enormous acanthosis and miliary abscesses throughout the hypertrophic rete as well as the corium are characteristic features

The reservoir of the infecting fungus is probably on certain plants. Infection from man to man occurs only under extraordinary circumstances. The only such case known is that of a physician who injured himself at the necropsy of a case of systemic blastomycosis (Evans after Martin and Smith⁶³⁴)

The age incidence has its peak between 20 and 40 years. Men are nine times as often infected as are women. The disease is far more common among the poorer classes⁶³⁴

The prognosis of the systemic cases is almost invariably fatal. The localized primary skin infection may take a chronic course but it will finally heal unless it becomes systemic which is unusual

Clinical diagnosis from the skin lesions is often possible. Other mycoses tuberculosis verrucosa syphilis and fungating granulomas must be ruled out. The detection of the organism in the pus of small abscesses microscopically or by culture will usually confirm the clinical diagnosis. For the microscopic examination the material is covered with a drop of 40 per cent KOH and examined in minimal light after at least ten minutes. A vaccine from heat killed fungi⁶³⁴ is used in the diagnosis and treatment

Treatment—Excision of small lesions may occasionally arrest the disease. Irritating substances such as caustics often make the condition worse. Potassium iodide in huge doses up to 25 Gm daily^{632 633} has often healed and often failed but it is nevertheless still the method of choice. Combination with X ray therapy and vaccine may be judiciously used in combination with potassium iodide which loses its effect after prolonged administration. Martin and Smith caution against the indiscriminate use of potassium iodide in hypersensitive cases. These cases should be desensitized by a series of vaccine injections

⁶³⁴Bu h J D Blastomycosis Arch Dermat & Syph 43 485 490 1941

CHAPTER IX

HELMINTHIC DISEASES

Trichinosis

It is now well established that trichinosis is a common human infection in the United States. A great number of post mortem diaphragm examinations conducted in various parts of the country^{636 640} have shown that 12 to 18 per cent of the cadavers harbor trichinae. The infection stems largely from inadequately cooked pork rarely from the meat of bears wild boars and some other large animals. A main source of infection of the swine is the practice of feeding them uncooked scraps of pork while trichinous rats play a minor role.⁶³⁷ On ingestion of trichinous meat the dormant and encysted worms are freed by the gastric juice. They propagate in the small intestine after one week. The young worms which are smaller than a red blood cell are carried by the circulation to the muscles. Here they grow and encapsulate and may live for as many as thirty years.

The clinical picture of human trichinosis depends on such factors as massive infection or small size of the patient tissues invaded general resistance and concomitant pathological conditions.⁶³⁷ Many cases pass symptomless or undiagnosed. The clinical course can be divided roughly into three stages (Davaine after Beeson⁶⁴¹) but it must be emphasized that this clearly defined sequence is seldom observed in practice. There is an initial gastrointestinal phase starting sometimes hours after the ingestion of trichinous meat. At the end of the first week it is followed by a stage of dissemination marked by prostration facial edema fever sweating and pain in the muscles of respiration mastication and the eye. After six weeks the disease passes gradually into the stage of encystment of the worms in the muscles while the severe symptoms ease up and the fever subsides. Edema muscular pains and anemia may persist for a long time. The average mortality which was very high in some German epidemics of the nineteenth century is probably less than 5 per cent of the clinical cases in the United States.⁶⁴² Most deaths occur from the fourth to sixth week and are due to myocarditis or bronchopneumonia.⁶³⁹ There are indications that existing infection protects against reinfection.⁶⁴³

⁶³⁶Hall M C and Collins B J. Studies on Trichinosis. Pub. H. alth. Rep. III 469-490 1937

⁶³⁷Hall M C. Studies on Trichinosis. Pub. H. alth. Rep. 62 539-551 1937. 63 1472 1486 1939

⁶³⁸Kerr I H Jacobs L and Cavillier F. Trichinosis. Post mortem Examination of 3 000 Diaphragms From Washington D C and Five Eastern Seaboard Cities. Pub. H. alth. Rep. III 836 855 1941

⁶³⁹Could S F. Trichinosis. Springfield Ill 1945 Charles C Thomas Publisher

Could S E. Method for Control of Trichinosis in the U S A. J A M A 129 1251 1254 1946

Beeson P B. Trichinosis—Clinical Manifestations. Lancet 1941 - 6 - 60

⁶⁴⁰Drummer H. Trichinosis. Connecticut M J 4 314-317 1940

⁶⁴¹Wyrens R O Wilsch J M and Magath T B. Trichinosis. J A M A 117 425-437 1941

The blood changes are characteristic. There may be severe anemia and leukocytosis. *Eosinophilia* is an almost invariable sign in the second stage. It may range from a few to 73 per cent⁴⁴⁴ and is considered the most reliable diagnostic sign⁴⁴⁵. However, eosinophilia may be missed or disappear in severe cases⁴⁴⁴.

A cutaneous *immediate urticarial reaction* with an allergen from digested trichinous meat has been developed by Bachman⁴⁴⁶. Besides the immediate response which appears within thirty minutes, a *delayed* reaction may occur after two days. This test is supposed to become positive in the third week of illness^{153 447 448}. The reaction is about as reliable as the precipitin reaction which becomes positive in the fourth week⁴⁴⁹ or as the complement fixation test⁴⁵⁰. Considering the frequency of trichinella infection, a positive skin reaction is only valuable if supported by other evidence of recent infection or if it has turned positive while the disease has been observed⁴⁴⁹. The test* may be negative in very severe cases^{159 451 452}. In all tests, group reactions against other common worm infections must be borne in mind⁴⁵³. For example, Fulleborn⁴⁴⁴ mentions a case of a patient infected with echinococcus who gave a positive reaction to echinococcus antigen as well as to antigen from *Cysticercus tenuicollis*, trichinella and strongyloides. There is also a common antigen in ascaris and trichinella⁴⁵⁴ and pinworm and trichinella⁴⁵⁵. Muscle biopsy (gastrocnemius) is rarely necessary. The muscle specimen should be pressed between two glass slides and examined at low power as is done in the testing of meat. Trichinae can occasionally be centrifuged from the stools, the bile, the arterial blood⁴⁵⁶ or the cerebrospinal fluid⁴⁵⁷.

Dermadromes.—The scarcity of cutaneous lesions is in agreement with the rarity of the presence of trichinae in the skin of experimentally infected mice⁴⁵⁸.

Edema of the eyelids is the most common, and in fact the only dermadrome which is seen in the majority of the cases. It is an early important sign of mus-

The allergen can be obtained from the National Institute of Health in Bethesda, Md., which also does the precipitin test on serum sent in for this purpose.

⁴⁴⁴ Murphy F D, James H B and Rastetter J W. Trichinosis. *93 Cases*. *Am J M Sc* 199 329-338 1940.

⁴⁴⁶ McNaught J B. Laboratory Procedures for the Diagnosis of Trichinosis. *Am J Clin Path Tech Sect* 11 87 1944.

⁴⁴⁸ Bachman G W. An Intradermal Reaction in Experimental Trichiniasis. *J Prev Med* 2 513 5 3 19 4.

⁴⁴⁷ McNaught J B. Diagnosis of Trichinosis. *Am J Trop Med* 10 161 102 1930.

⁴⁴⁹ Hall A A. Trichiniasis. Use of the Bachman Intradermal Skin Test. *Ann Int Med* 10 1544 1550 1937.

⁴⁵⁰ Kaufman R E. Trichiniasis. Clinical Considerations. *Ann Int Med* 11 1431 1480 1910.

⁴⁵¹ Gaase A. Trichinosis. A Rodignosis With Complement Fixation. *München med Wchnchr* 111 473-474 1941.

⁴⁵² McNaught J B. Medical and Public Health Aspects of Trichinosis. *Texas State J Med* 23 232 55 1947.

⁴⁵³ McNaught J B, Beard R R and Myers J D. Diagnosis of Trichinosis by Skin and Precipitin Tests. *Am J Clin Path* 11 195-201 1941.

⁴⁵⁴ Jadassohn W. Die Immunologie der Haut. *Hanb f H u Gk* 2 418 1937.

⁴⁵⁵ Fulleborn E. Diagnostisch Cutaneaktion bei Helminthenkrankheiten. *Allg Wehnschr* 7 8 0 1929.

⁴⁵⁶ Dammin C J. Trichinosis—Report of a Case With Demonstration of Larva in Arterial Blood. *New England J Med* 224 3 7360 1941.

⁴⁵⁷ Maass E A and Otto C F. Occurrence of Trichinella Spiralis Larva in Tissues Other Than Skeletal Muscles. *J Lab & Clin Med* 27 1344 1347 1941.

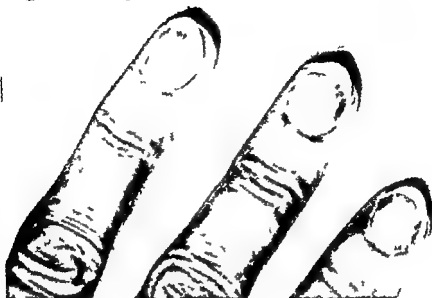


Fig 90 — Splinter hemorrhages in trichinosis (Courtesy McNaught J B. *Am J Trop Med* 1939)

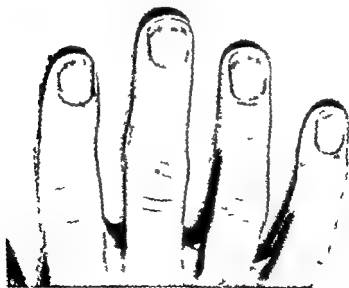


Fig 91 Trichinosis Splinter hemorrhages arranged in cross lines indicating simultaneous genesis (Courtesy D. Breason)

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Morphy F D, James H D and Rastett J W. Trichinosis. 21 Cases. Am J Hyg 26: 329-338 1940.

⁴⁴¹McNaught J B. Laboratory Procedures for the Diagnosis of Trichinosis. Am J Clin Path Tech Sect B 17: 93 1944.

⁴⁴²Bachman G W. An Intradermal Reaction in Experimental Trichinosis. J Prev Med 2: 513-53 1924.

⁴⁴³McNaught J B. Diagnosis of Trichinosis. Am J Trop Med 28: 181-187 1939.

⁴⁴⁴Hall A A. Trichinosis. Lab of Dr. Bachman. Intradermal Skin Test. Ann Int Med 29: 1514-1550 1917.

⁴⁴⁵Hauffman R F. Trichinosis. Clinical Considerations. Ann Int Med 12: 1431-1460 1940.

⁴⁴⁶Gaase A. Trichinosis. % re diagnosis With Complement Fixation. München med Wochenschr 88: 473-474 1941.

⁴⁴⁷McNaught J B. Medical and Public Health Aspect of Trichinosis. Texas State J Med 29: 252-255 1947.

⁴⁴⁸McNaught J B, Beard R B and Myers J D. Diagnosis of Trichinosis by Skin and Precipitin Test. Am J Clin Path 11: 295-301 1941.

⁴⁴⁹Jadawohn W. Di Immunologische Reaktion. Handb d Hyg u Inf 2: 418-197.

⁴⁵⁰Fulleborn F. Diagnostische (serologische) Helminthosenreaktion. Klin Wochenschr 80: 19-24.

⁴⁵¹Dammin C J. Trichinosis. Report of a Case With Demonstration of Larva in Arterial Blood. New England J Med 221: 35-360 1941.

⁴⁵²Maus H A and Otto G F. Occurrence of Trichinella spiralis Larva in Tissues Other Than Skeletal Muscles. J Lab & Clin Med 27: 1345-1347 1941.

Ancylostomiasis (Hookworm Disease)

Ancylostomiasis (Hookworm Disease) The hookworms⁶⁶⁴ for medical purposes the genera *ancylostoma* and *necator* are duodenal human parasites whose larvae leave the bowel with the feces in great numbers. These larvae are about 0.5 mm long. They enter the body through the unbroken skin especially the thin skin of the instep area and are carried by the lymph and blood to the lungs from where they follow the bronchotracheal tree into the larynx, pharynx and finally the gastrointestinal canal (Looss after H. Bruns⁶⁶⁵) to their living and breeding place the duodenum. The hookworms are found chiefly in warmer climates. They have caused epidemics in warm countries among barefooted workers on rice, tea, mulberry and similar plantations and in colder climates among miners working in the warm and humid shafts.

The disease is common in the southern section of the United States and especially in Puerto Rico. The infection causes a severe, often fatal, progressive anemia and involvement of many organs.

Dermadromes—When the larvae penetrate the skin of the feet they cause itching, vesicular dermatitis and possibly secondary infection. However, a controversial point is to what extent hookworm causes the ground itch of the south or mazamorra of Puerto Rico and Central America, a common eczematous condition of the feet. Fulleborn⁶⁶⁶ denies that the majority of the ground itch cases have anything to do with ancylostomiasis. It is claimed that *Necator americanus* is more likely to cause ground itch than *Ancylostoma duodenale*.⁶⁶⁸

If the hookworm infection has become fully developed, *pruritus*, marked dryness of the skin and hair, reduced perspiration on exertion and heat and burning of the palms are reported to be troublesome symptoms (Ashford and King after Fulleborn⁶⁶⁶). The features are reported to become blurred and slightly puffy, shift of pigment takes place⁶⁶⁶ and persistent acne may occur. A butterfly shaped pigmentation over the bridge of the nose has at times been thought to be diagnostic of schistosomiasis but this is not true since such pigmentations occur also in other infections (bilharziosis) and probably also in various nonhelminthic conditions. The diagnostic value of minute black or brown spots on the side of the tongue or on the lips in patients with hookworm is doubtful.^{667, 668}

Creeping eruption caused by the larvae of *ancylostoma braziliense* and other nematodes is not always restricted to the skin.^{669, 670} It may, like other worm

⁶⁶⁴Fulleborn F. Haut und Helminthen. Handb. d. H. u. G. II. 1. 703-800, 1931.

⁶⁶⁵Bruns H. Di. Ancylostomiasis in der gemässigten Zone. Handb. d. path. Mikroorg. 2. 907-914, 1922.

⁶⁶⁶Daemann G. Di. Ancylostomiasis in den Tropen und Subtropen. Handb. d. path. Mikroorg. 2. 949-954, 1922.

⁶⁶⁷Sutton R. L. and Sutton R. L. Jr. The area of the skin. St. Louis, 1939. Th. C. V. Mosby Co.

⁶⁶⁸Jockers H. Pigmentation of the skin. New England J. Med. 221. 88, 100, 122, 136, 181, 189, 1943.

⁶⁶⁹Millsbaugh J. A. and Compayrac L. M. Hookworm Infection. Creeping Eruption. Infestation With *Ancylostoma Braziliense*. U. S. Nav. M. Bull. 68. 393-398, 1941.

⁶⁷⁰Kirby-Smith J. L., Doe W. H. and White G. F. Creeping Eruption. Arch. Dermat. & Syph. 13. 137-175, 1926.

The diagnosis rests on the finding of worms or their ova. The latter are best collected with a few energetic strokes in a peripheral direction from the anus with a cellophane (Scotch tape) tipped swab⁵⁷⁹. The cellophane is then examined on a slide moistened with water and covered with a cover slip. A skin test with enterobius antigen may be helpful^{576, 580}. Brady and Wright⁵⁸¹ were unable to find any typical cutaneous lesions in 200 controlled cases. In a series of tests Brady and Wright⁵⁸¹ found that gentian violet given by mouth was superior to other methods. The dosage of the drug for adults was two 32 mg tablets three times a day before meals and for children 10 mg a day for each year of their apparent not actual age the total amount being divided into three doses.

FILARIASIS

Wuchereria (Filaria) bancrofti is a nematode of the warm climates. The adult worm which is as thick as a strong hair and several centimeters long lives in the human lymphatics and produces tremendous numbers of microfilariae which are about 0.3 mm long and no thicker than a red blood cell. These microscopic worms live in the blood appearing in great numbers at night in the peripheral blood and retreating at day into the visceral arteries. The microfilariae pass part of their development in various mosquito vectors but they are brought back into man to complete their life cycle. According to Manson-Bahr⁵⁸², Fülleborn⁵⁸³ and other authorities on tropical medicine the microfilariae in spite of their number have no pathogenic properties while in a certain proportion of instances the obstruction of lymphatics caused by the adult worm causes lymphedema, lymphatic varicosities and elephantiasis. The monstrous enlargements of legs, mammae, scrotum and other parts are well known pictures of tropical pathology. The lymph stasis inflammatory reaction, scarring and calcification caused by the adult worms may be permanent. The lesion is likely to become infected with hemolytic streptococci causing the repeated erysipelatoid attacks which are the more immediate cause of elephantiasis^{584, 585}. Other authors believe that elephantiasis may develop without acute attacks⁵⁸⁴. Grace⁵⁸⁵ feels that there is no evidence that *Wuchereria (Filaria) bancrofti* plays any part in the production of the attacks of lymphangitis. Recent observations on military personnel in endemic areas⁵⁸⁶ have shown that acute lymphangitis of arms or legs and acute funiculitis or epididymitis with little fever or general symptoms are the outstanding early clinical symptoms. Peculiar features are a centrifugal lymphangitis which may work down from the

⁵⁷⁹ Hall M C. Studies on Oxyurias. I. Types of Anal Swabs and Scrapers. Am J Trop Med Hyg 445-453 1937

⁵⁸⁰ Tsuchiya H and Bauerl in T C. Intradermal Test as Aid in Diagnosis of Entrobiasis. J Lab & Clin Med 24 6 763 1939

⁵⁸¹ Brady F J and Wright W H. Oxyuriasis. 100 Cases. Am J M 11 198 367-377 1939

⁵⁸² Low C C. Pathology of Filariasis. J Stat Med 29 594-598 1931

⁵⁸³ Brug A L. Filariasis and Elephantiasis. Nedert tijdschr v geneesk 76 2772-2776 1931 Zbl 43 149

⁵⁸⁴ Fülleborn L. Clinical Studies of Filariasis. Geneesk tijdschr v Nederl Indië 72 647-658 1933

⁵⁸⁵ Grace A W. Filariasis. Tropical Lymphangitis and Abscesses. J A M A 123 462-466 1943

⁵⁸⁶ Thompson E J, Rifkin H and Zarrow M. Early Filariasis in Young Males. J A M A 129 1074-1080 1943



Fig 02 —Microfilaria of *L. loa* in blood film ($\times 1700$). Actual length 165 microns. The only successful preparations were made from the blood taken from a Calabar swelling on the forearm in the late afternoon. Giemsa stain. (From Guy W H Cohen M and Jacob F M Arch Dermat 1943)



Fig 03 —Calabar swelling. From Guy W H Cohen M and Jacob F M Arch Dermat 1943)

upper arm to the waist and lymph nodes in unusual sites for example the tip of the ileum the midarm and the region of the serratus and teres muscles. Centripetal lymphangitis occurs also. In the chronic stages the skin manifestations are due mainly to the enormous lymphatic varicosities and enlarged lymph nodes which may cause dome shaped pseudovesicles of the skin. A positive reaction to an intradermal injection of 1:4000 *filaria antigen* is considered diagnostic.⁴⁸⁸ Other worm infections do not respond to a dilution higher than 1:2000. *Filaria loa* an African species transmitted by a fly migrates in the connective tissue often near or in the skin or beneath the bulbar conjunctiva producing the so called *Calabar swelling* these lesions appear on the forearms or less commonly over the ankles or on the face. They probably represent an allergic

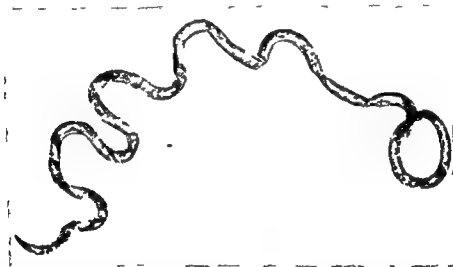


Fig 91 — *Filaria of L. loa* (X8) actual length 43 mm. Adult worm removed from the conjunctiva of a missionary returned from the Cameroon Africa. Note the nuclear structure and the twist at the caudal end. (From Guy W H Cohen M and Jacob F M. Arch Dermat 1943.)

reaction to the worm or its products. The worm or calcified remnants of it have been demonstrated by roentgenogram.⁴⁸⁷ The swellings are usually rather painless but sometimes itchy. They disappear after a few days or rarely after weeks⁴⁹ only to recur somewhere else.⁴⁸⁸ Scabies like itching eruptions are known as filarial prurigo or gale filarienne.⁴⁸⁹ Besides the mentioned skin tests complement fixation reactions in filariasis have been developed.^{490,491} Eosinophilia may reach 24 per cent.⁴⁹²

⁴⁸⁷Griegel F H W. Filariasis. Calabar Swelling With Radiologic Observations. J Trop Med 42 11-71 1940.

⁴⁸⁸Guy W H Cohen M and Jacob F M. Infection With *Loa Loa*. Arch Dermat & Syph 47 63-767 1943.

⁴⁸⁹Stefanopoulos G. Filarial Prurigo or Gale Filarienne in Calabar. Due to *Loa Loa*. Trop Dis Bull 40 85 1943.

⁴⁹⁰Fahmy N H. Skin Test and Complement Fixation in Filariasis. Tr Roy Soc Trop Med & Hyg 25 20-1 1931.

⁴⁹¹Rodhain J and Dubois A. Intradermal Reaction in Human Filariasis. Tr Roy Soc Trop Med & Hyg 25 3 7-35 1931.

⁴⁹²Low G C. Skin Conditions Found in *Loa Loa* Infections. J Trop Med 37 3 9-3603 1934.

An eosinophilic disease with migratory edematous swellings which has lately been observed in small epidemics in Palestine probably is related to Calabar swelling⁴³⁷

Onchocerciasis

Onchocerca is a nematode which resembles filaria in many respects. The life cycle which is not fully understood is partly spent in flies of the genus *Simulium*. The adult worms and great numbers of microfilariae live in cystic tumors (onchocercomas) of the subcutis. The majority of the patients with onchocercomas present no demonstrable cutaneous manifestations. However microfilariae have been found in great numbers in apparently unaffected skin⁴³⁸ as well as in the blood. The onchocerca nodules are pea to almond sized and occur most frequently over the skull which they may perforate along the costal arches and about the joints where they may simulate joint articular nodes. There is an African type caused by *Onchocerca volvulus* and a Central American type caused by *Onchocerca caecutiens*. The latter is restricted to parts of Guatemala and Mexico. The American onchocerciasis is of importance because of the keratitis and iritis which accompany many cases and which may lead to blindness (onchophthalmia)^{439 440 441}. Acute febrile erysipelatoid swellings of the face and of the limbs characterized by hardness and a greenish hue and transitions into chronic edema occur among patients with onchocerca nodules (Robles after Fulleborn⁴⁴²). In both types of onchocerciasis the skin may become dry itchy infiltrated and constricted (onchodermatitis). This pruriginous phase may look much like scabies⁴⁴³ or neurodermatitis⁴⁴⁴. The microfilariae of *Onchocerca volvulus* can be found in the irritated skin. Itching seems to be caused by allergic phenomena rather than by the active moving of the worms since heavily infected skin was found without associated pruritus⁴⁴⁵.

Dracunculiasis or Dracontiasis (Guinea Worm)

The guinea worm (*Dracunculus medinensis* or *Fuellebornius medinensis* formerly called *Filaria medinensis*) is in its larval stage a parasite of some microscopic crustacea of the genus cyclops which infests man through drinking water or through direct entrance into the skin. After one year, the adult fertilized female which is one yard long and about as thick as a thread appears under the skin sometimes preceded by fever and urticaria⁴⁴⁶. A dome shaped blister later an ulcer indicates its end. The lesion varies in diameter from 2 to 7 mm⁴⁴⁷. On

⁴³⁷Leffkowitz M and Suklinski A. Clinical Picture of Eosinophilic Disease With Cutaneous Manifestation. *Harvard Bull* 38: 12, 1945.

⁴³⁸Goldman I. Am J Trop Med Hyg 127: 34-39, 1944.

⁴³⁹Hoffman C. and Vargas L. A communication sur les cas de la onchorose de Chiapas. *Rev Mex de Med* 31: 1, 147, 1931. 21: 41, 795.

⁴⁴⁰Fuller F. I. and J. H. J. Hantersbach. *Journal de la Société de Médecine de la Guinée* 1940. 1: 1. Zusammenfassung über die Heilung der Onchorose durch die Verwendung von Antikörpern. *Arch f Dermat u Syph* 164: 16-34, 1931.

⁴⁴¹Anderson C. and Leitcher J. Onchocerciasis (Guinea Worm) in Tunisia. *Arch et Inst Pasteur de Tunis* 29: 103-112, 1940.

⁴⁴²Lowenthal L. J. A. Onchocerciasis (Guinea Worm) in Tunisia. *Ann Trop Med* 27: 147-148, 1943.

douching with cool water the worm will often protrude from a small hole and expell a fluid containing thousands of embryos

The premonitory urticaria and pruritus and also asthma and diarrhea are probably caused by the same allergens in the excreta which cause the blister and ulcer. The microfilariae do not have the toxic or allergenic effect of the adult worm⁶⁹³ which if injured or dead sometimes causes severe reactions. The therapy consists in cautious and patient extraction of the entire adult worm which takes about two weeks. This requires a certain technique which can be found in the textbooks on tropical diseases.^{5 9 548 700}

Cysticercosis

Normally the adult tapeworm (usually *Taenia solium*) is a parasite of the human ileum. Its eggs must get into the stomach of the swine where the hatched embryos travel to the points of encapsulation. Occasionally man is the intermediate host instead of the pig. Then he will harbor the encapsulated larvae most often in the brain and the eye only in 6 per cent of the cases in the subcutaneous tissues. The subcutaneous or cutaneous cysticerci are cysts of from one to several centimeters in diameter. They are round or oblong and are freely movable in the subcutaneous tissue. The cysts are of elastic hardness and non tender numbering a few or several thousands. The inflammatory reaction is insignificant. If they are diagnosed they may help to explain other symptoms caused by cysticercosis of internal organs.^{701 702} The prognosis of cysticercosis of the skin per se is favorable. The cysts usually stay without change and sometimes disappear spontaneously. The huge *echinococcus* cyst is the larva of a small tapeworm of the dog. The disease is very rare in the United States. An intracutaneous test with liquid from the cysts (Casoni test) and a complement fixation test are reliable.

The larvae of some tropical cestodes (*Sparganum proliferum*) may cause small acne like cutaneous cysts besides severe involvement⁷⁰³ of almost the entire system in some of the few studied cases.⁶⁶⁴

Bilharziasis

The adult worms of *Schistosoma hematobium* live in pairs in the portal system of man producing eggs which appear in the feces and in the urine. In water

⁶ Fairley N H and Liston W C. Studies in the Pathology of Dracontiasis I Indian J. M. Res. Arch 11 915 93 19 4

¹⁰¹ Fairley N H. Studies in Dracontiasis VI Indian J. Gaz 59 4 9-434 19 1

¹⁰² Takamatsu H. Generalized Cysticercosis. Zentr. bl. f. allg. Path. u. path. Anat. 72 4 1939

⁷⁰³ Tanasescu I and Rapceiu E. Fil. Falt on Cysticercus bovis im Unterhautgewebe des Menschen. Virchow Arch. B. path. Anat. 301 55 4 1939

⁷⁰⁴ Plank W. Die ische Parasiten der Haut II. Abh. d. H. u. Ch. 1 467 514 19 7

⁷⁰⁵ Brailford J F. Unreog. I. Cysticercosis. Lancet 1 197 1 9 194

⁶⁶⁴ Hu C H. Oo-h. E. I. a. d. F. a. r. C. N. Subcutaneous Cysticercosis Cellulosa In Man. Flv. Cases. Arch. Dermat. & Syph. 21 777 49 1930

⁷⁰⁶ Atiles C W and Taylor L. The Larval Cestode (*Sparganum manaudi*) of Man Which May Possibly Occur in the United States. Troops Bull. 35 Bureau of Animal Industry U. S. Dept. Agric. Washington 190

they develop into larvae (cercariae) which are able to enter the human body through the skin

Bilharziasis is predominantly a urinary disease. It is a public health problem of great importance in Egypt, Japan, China and other countries especially where work in flooded rice fields brings about the exposure to infection with cercariae

Dermadromes—The dermadromes are of little importance in comparison with the frequent and severe bladder involvement. The skin in the neighborhood of the urinary fistulae may contain huge numbers of often calcified eggs. The irritation from urine, pus and infestation may give rise to *papillomas* of the anal and genital region which occasionally become malignant. Sinderson¹⁰⁷ found in 20 per cent of the schistosomiasis (hematobium) cases that he observed in Iraq a sometimes reticulated, well defined butterfly shaped *hyperpigmentation* over the bridge of the nose and the cheeks. He believes that it is caused by a photosensitization of the skin under the influence of the worms (see under ancylostomiasis)

The entering cercariae of schistosoma hardly cause¹⁰⁸ dermatitis while the cercariae of otherwise innocuous trematodes have been held responsible for many epidemics of *swimmers itch*

¹⁰⁷Sinderson H. C. Anomalous Pigmentation in Schistosomiasis. Tr. Roy. Soc. Trop. Med. 23: 633-634, 1930

¹⁰⁸Lutz A. and Lutz O. A. Bilharziasis oder Schistosomuminfektion. Handb. d. path. Mikroorg. 6: 873-906, 1939

CHAPTER X

TUBERCULOSIS

The elementary facts concerning the tubercle bacillus and the general pathology of tuberculosis are so well known that it does not seem necessary to discuss them except for some phenomena which are of special importance in the pathogenesis of the cutaneous manifestations of internal tuberculosis

If the skin of a *normal*^{706 709 711} guinea pig is inoculated with tubercle bacilli the small wound heals primarily After a week an inflammatory reaction sets in A papule develops which during the third week forms an ulcer There is little tendency to heal and some ulceration or infiltration usually still exists when the animal dies of generalized tuberculosis During the second week lymphangitis and lymphadenitis are marked The histological picture shows at first an inflammatory reaction with many groups of tubercle bacilli During the third week tuberculoid structures start to form and the number of bacilli decreases so that only occasionally can single rods be found Tuberculin skin tests start to become positive about ten days after the infection Within four weeks the entire skin has become sensitized⁷¹⁰

If the identical inoculation of tubercle bacilli is done in the skin of a guinea pig which at least four weeks *previously had been infected* with tuberculosis an acute hemorrhagic edematous and sometimes necrotic reaction starts within twenty four hours reaches its height on the second day and then subsides rapidly After about ten days a necrotic hemorrhagic crust is thrown off After three to four weeks the lesion is usually healed There is no additional lymphadenitis and no further ulceration The histological examination reveals an acute inflammation The scab which contains the bulk of the bacilli comes off the underlying erosion heals and is soon covered with normal epidermis Some times tuberculoid structures are formed earlier than in the primary inoculation It must be emphasized that this sequence of changes after primary and super infection known as *Koch's fundamental phenomenon* is subject to many variations and that great skill and experience are required to produce it in complete clarity This is particularly true⁷⁰⁸ of the experimental hematogenous i.e. *intracardial* infection of the guinea pig

Two weeks after the intracardial injection of tubercle bacilli normal animals develop a papulo squamous rash and die from generalized tuberculosis after four to five weeks Tuberculous guinea pigs however show during the second day a follicular rash which heals quickly after a latency of about two weeks

⁷⁰⁶Lewinowsky F: III Tuberkulose d. Haut II Klin 1916 Julius Spring

⁷⁰⁷Sulzberger M B and Wise F: Tuberculin in the Dermatological Considerations Clin Noth Amrica 11 1555 1931

⁷¹¹Matenfeld H: Neuere Ergebnisse auf dem Gebiet der Hauttuberkulose Die extraprimäre Tuberkulose Vienna 1930 Urban and Schwarzenberg

some papulocrustous lesions appear which heal spontaneously. The microscopic picture of the hematogenous lesion in the first infected animal is that of an inflammatory reaction of nonspecific character with abundant bacilli. The hematogenous lesions in superinfected animals are decidedly tubercular in structure consisting of epithelioid and typical giant cells. There is perivascular necrosis but hardly any bacilli can be detected. The lesions are often found in the follicular plexus³⁶⁶. Similar tuberculoid lesions can be produced by the intracardial injection of killed tubercle bacilli.

The interpretation of these experiments and many variations has been formulated by J. Jadassohn¹⁰ and his pupils especially Lewandowsky in a rule which has been amply confirmed not only in tuberculosis but also in many other infections. This so called *law of J. Jadassohn and Lewandowsky* states that unchecked growth of microbes causes nonspecific inflammation. Where however microbes are locally and not too rapidly destroyed by the immunobiologic defensive reaction tuberculous structures develop.* This law applies to the products of microorganisms.

Koch's fundamental phenomenon has been found valid in the human pathology. If the skin of a person who has not had tuberculosis before is infected with tubercle bacilli a lesion characterized by rapid ulceration, lymphangitis and lymphadenitis and abscess formation develops in the course of one to two weeks.^{1, 718} This syndrome which is best known from the cases of circumcision tuberculosis⁷¹ but also from other traumatic infections^{719, 720} is called the primary complex of tuberculosis of the skin.

The number of bacilli in the ulcer is large so that they can be found in the direct smear. The tuberculin reaction is negative in the early stages but becomes positive three to eight weeks after the cutaneous infection (E. Lowenstein after E. H. Urbach^{119, 121}). The tuberculous *primary complex* of the skin is much rarer than its pulmonary counterpart the Ghon tubercle. Approximately one out of 750 cases of tuberculosis starts in the skin.^{120, 122, 124}

Tubercle bacilli—for that matter also other microbes—spread very rapidly from a skin infection. Excision of a primary skin infection does not prevent

For a list of publications on experimental tattooing see Gulsberg in *Dermatologic Allergy* 79 (1971) 4 of monographs prepared with the direction of Drs G. M. H. and W. J. L. (1971).

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² Mithun R P Primary complex of Tuberculosis of the Skin A few of the features

Arch Demat & Syph 32 53 001 1935
O Leary : A m : Har L on M W I oculation Tuberculo : A m De mat & Syph 31
321 390 1941

Wolff E. Über die umförmige tuberkulöse Herdbildung. Wehrh. 131 1911
 Flück hat in L. (1911) Nachuntersuchung tuberkulöser Herde bei 1821 Pavi. 3 1 19 107

¹¹Phillips H. H. Th. Primary Cutaneous Tuberculosis (comp. x J. A. M. 108 071 035 1917)
¹²Schacharman C. Primary Tuberculosis of Skin in Child = Granuloma Formation of

Lupa Arch # 141 b 118 33 3 1970
 11/11/1970 H F All grey and heat cane 1: Tuberculous Journal Jan 1 42 20 211 101

Chon A Tb : loss of complex of Human Tuberculo le Am R v Tuberc 7 314 10 3

Sallick M A Primary Cutaneous Complex Isolation Tuberculosis J Mt Sinai Hosp 4:50 1939

systemic infection. Lowenstein was unable to prevent the generalization of a tuberculous infection from the hindleg of a guinea pig when he amputated the limb five minutes after the inoculation. A great number of similar observations have been made³⁶⁶ showing that a truly local skin infection hardly exists. The primary tuberculous complex of the skin is of little practical though of great theoretical importance. The majority of the tuberculous skin infections differ in two important points from the primary complex. They occur in an already tuberculous and allergic organism and they are overwhelmingly autogenous and usually hematogenous. These two facts help to explain many of the characteristics of the tuberculodermas.*

The great variety of clinical pictures of cutaneous tuberculosis is caused by the fact that neither the virulence of the tubercle bacilli nor the defense mechanisms of the human organism are powerful enough to bring about either a complete healing or a fatal course. The tuberculous infection can be compared to a war of position and attrition. Jadassohn believed that superinfection is the most important factor in developing lupus from a tuberculous infection. This has been widely accepted though some authors at least in some cases have placed more emphasis on the differences in the reactions of the infantile and adult human skins. Volk³⁶⁸ sees an analogy in the difference of the primary tuberculous skin infection of the guinea pig which almost always develops an ulcerative and later generalized and fatal tuberculosis and the cutaneous infection of the rabbit in which the skin infection resembles lupus remains localized and has a marked spontaneous healing tendency.⁷¹⁷

The bovine type of the tubercle bacillus causes about 13 per cent of all cases of skin tuberculosis.⁷ It has already been said that the *tuberculin skin test* becomes positive from three to eight weeks after the infection. The positive reaction is evidence of allergy against the tubercle bacillus and its products but it does not indicate immunity or resistance. The complete breakdown of the resistance as encountered in miliary tuberculosis and cachexia may be accompanied by a breakdown of other systemic functions e.g. the ability to react with inflammation to the tubercle bacillus. In other words the tuberculin reaction may become negative. This phenomenon is called *negative energy*. However measles influenza and other infections some forms of skin tuberculosis and especially the sarcoids⁷ 3 729 730 may prevent a positive reaction in an active

The term tubercloid has been avoided since it is confusing and unnecessary. It can be considered accepted that all tuberculids are tuberculosis (Sulzberger and Goodman⁷²⁹) and that microorganisms are demonstrable in practically all tuberculids (Wise and Sulzberger⁷²⁶).

⁷²⁶Sulzberger M H and Goodman J. Tuberculodermas. *M Clin North America* 20: 975-1007 1936.

⁷²⁷Wise F and Sulzberger M H. Yearbook of Dermatology Chicago 1935. The Yearbook of Dermatology p 373.

⁷²⁸Kallous P and Kallous-Deffner L L. Über Allergie- und Immunitätsverhältnisse bei Hauttuberkulose. *Zbl Bakt* 48: 773-99 1933.

⁷²⁹Dietz J. Über die Typen der Tuberkulobacillen (TB) bei Hauttuberkulose. *Arch f Dermat u Syph* 179: 360-376 1939.

⁷³⁰Ziller and Häsel. Hauttuberkulose in ihren Beziehungen zur Tuberkulose innerer Organe. *Frgbn d ges Tuberk Forsch* 6: 435 1934.

⁷³¹Finer M. Non-Casati's Tuberculosis. *Am Rev Tuberc* 37: 690 1934.

way by production of inhibiting substances which are called anticutins^{731 73} This is called *positive anergy* In such cases the resistance to infection e g with the bacillus Calmette Guérin may be very high⁷⁴ The conception of positive anergy is based on the noncachectic cases with positive tuberculosis and one of the mentioned conditions especially the sarcoids in which the tuberculin reaction is negative^{733 734}

The methods of skin testing for tuberculin allergy are the same as those used in testing other kinds of allergic conditions

1 The intracutaneous injection^{735 738} This test is very accurate in J Jadassohn's graded quantitative method which consists of the simultaneous intradermal injections of 0.1 c.c. of dilutions of old tuberculin—Koch (OTK) in concentrations of 1:1 000 000 1:100 000 1:10 000 and in some cases 1:100 and 1:10 and control saline wheals⁷³³ More often purified protein derivative (PPD) is used This is available in convenient tablets of two strengths which have to be dissolved in 1 c.c. of diluent One tenth cubic centimeter of fresh first strength solution (0.0005 mg) is injected first If no reaction within 48 hours occurs 0.1 c.c. of fresh second strength solution (0.005 mg) is injected into the other arm

2 The scratch or abrasion test (von Pirquet)⁷³⁷ with OTK

3 The injection of a 50 per cent tuberculin linolin saline⁷³⁸

4 The patch test^{739 740}

For the technique of these tests the reader is referred to textbooks of allergy and tuberculosis for comparative evaluation to E Friedman M H Black and A L Esserman⁷⁴¹ M Sulzberger and F Wise⁷⁴²

The patch test is a convenient and sufficiently reliable method for preliminary information Urbach⁷³⁹ advises following up a patch test which is negative after one week with the more sensitive Mendel Mantoux test In all tests the reaction can be considered positive if an inflammatory papule of at least 5 mm in diameter develops The papule reaches its height in forty eight to seventy two hours and then slowly fades Immediate reactions are not specific

⁷³¹Kogoj Fr Hauttuberkulose Ter Zprawy 6 137 189 = franz Zusammenfassung 100 107 1074 Zbl III 509

⁷³²Pinn M Wiles M and Cohen A C Procutins and Anticutins Yale J Biol & Med III 459-463 1943

⁷³³Hartstein H and Noll R Statistische Untersuchung über die Tuberculin Reaction Arch f Dermat u Syph 158 409 1939

⁷³⁴Loewy H Boeck's Sarcoid and Lupus Pernio Dissertation Breslau 1911

⁷³⁵Mindel F Die von Pirquet'sche Hautaktion und die intravenöse Tuberkulinbehandlung Med Klin 4 407-404 1904

⁷³⁶Mantoux C Intradermo-Tuberkulin Reaction Münch m med Wchnschr 53 2117 1904
⁷³⁷von Pirquet C Tuberkulindiagnose durch cutane Impfung Berl klin Wchnschr III 644 1907

⁷³⁸Moro M Über eine diagnostisch verwertbare Reaktion der Haut auf Einnahme mit Tiercutinsalbe Münch m med Wchnschr 53 216 1904

⁷³⁹Nathan E and Kailes P Leberineoplastische Tuberkulinreaktion bei Hauttuberkulose Klin Wchnschr 1931 II 7397-7399

⁷⁴⁰Vollmer H and Goldberg F F W A New Tuberculin Patch Test Am J Dis Child 54 1019 1937

⁷⁴¹Friedman E Black M H and Esserman A L Tuberculin Tests Am J Dis Child 46 55-65 1933

A *positive reaction* in children under seven years is generally a sign of active tuberculosis. Beyond seven years the positive test must be correlated with the clinical picture. In adults a positive test does not prove more than the well known fact that almost everybody once in his life becomes infected with tuberculosis. In the vast majority of the cases the disease becomes arrested after the primary stage leaving behind an allergy to tuberculin.

A *negative tuberculin test* especially the Mendel Mantoux test must with the mentioned exceptions be interpreted as indicative of the absence of a tuberculous infection of more than 8 weeks.

Hematogenous Skin Tuberculosis

Skin tuberculosis may develop by ectogenous inoculation into the skin and by endogenous infection. The tuberculosis verrucosa cutis of the hands in slaughterhouse workers, the postmortem wart and the lupus of the buttocks in small children who sit on the floor of a tubercle bacilli infected room are examples of ectogenous tuberculous skin infection. The endogenous infection of the skin plays a more important part. Endogenous lupus by contiguity from underlying tuberculous lymph nodes especially of the neck is a common occurrence in countries where skin tuberculosis is more frequent than in America. The lymphogenous spread of lupus is known. However compared with these ways of infection the hematogenous tuberculous infection of the skin is far more important. Foci of tuberculous infection which are capable of releasing tubercle bacilli into the bloodstream are very common. Even old calcified lymph nodes may still contain virulent tubercle bacilli as has been shown in autopsies of patients who for many years suffered from hematogenous crops of lupus. It is more difficult to explain why there is so little hematogenous skin tuberculosis in view of the frequency of the foci and of the bacilli in the blood than it is to give reasons for the hematogenous nature of many cases of cutaneous tuberculosis. It can be considered a fact that more than 50 per cent of the lupus cases are caused by hematogenous infection⁷² mostly from pulmonary or lymphatic foci.⁷³

The *relationship of pulmonary tuberculosis to cutaneous tuberculosis* has been the subject of many investigations. Pulmonary tuberculosis has been found existing simultaneously with skin tuberculosis especially lupus vulgaris in percentages differing as widely as 8 and 90 per cent. An analysis of 300 lupus cases in Münster, Germany⁷⁴ showed 12 per cent more or less active and 60 per cent inactive pulmonary tuberculosis while in a control group of about 5000 German university students only 1 per cent active and 18 per cent inactive lung cases could be found. St. Epstein⁷⁵ determined 16 per cent as the incidence of active pulmonary tuberculosis in 200 lupus patients. In 429 fatal lupus cases visceral usually pulmonary tuberculosis was the cause of death in

⁷²Krehan, H. Untersuchung über Hauttuberkulose. Würzburg. Abh. Bd. 27. H. 3. 1931.

⁷³Rauschke, J. E. Tuberculosis of the skin. Arch. Derm. & Syph. 29. 393-408. 1934.

⁷⁴Wintreiss, W. Lung abefunde bei 300 Lupus kranken. Ztschr. f. Tub. 70. 54-59. 1934.

⁷⁵Epstein, St. Tuberculosis of Lung in Patients With Sarcoidosis, Granuloma Annulare and Lupus Erythematosus. Arch. Dermat. & Syph. 42. 1-10. 1940.

48 per cent ⁷⁴⁶ From these and many other statistics it can be concluded that the incidence of lung tuberculosis in lupus is a high one. On the other hand the percentages of skin tuberculosis in very large groups of tuberculous patients has always been found low 0.2 per cent ⁷⁴⁷ 1 per cent in 27 540 cases ⁷⁴⁸ less than 1 per cent in 18 000 cases ⁷⁴⁹ This compares well with many older statistics ⁷⁵⁰ and seems to bear out the old rule that lupus patients often become consumptive but that consumptives rarely develop lupus. While the figures seem to be very low the incidence of skin tuberculosis is still about 1 to 3 times higher in patients with pulmonary tuberculosis than in a comparable normal group. Similar tendencies as in the relationship of lupus and pulmonary disease prevail in its relation to surgical tuberculosis. Among 275 lupus cases were 16 per cent with bone or joint tuberculosis while among 371 cases with tuberculosis of the bones and joints only 5 per cent had lupus ⁷⁵¹. The isolation of tubercle bacilli from the blood either by animal inoculation or by culture with the Lowenstein method has recently been more often successful than was held possible before. It is true that many observers could not obtain the same results as Lowenstein ⁷². The positive findings however carry more weight than the negative ones. Kren ⁵ could show that if blood culture of patients with lupus vulgaris erythema induratum and lupus erythematosus was done more than seven times positive cultures could be found in all cases. The frequently negative blood cultures are most likely due to technical difficulties to unfavorable time of testing and to the too small numbers of the investigations. In Kren's ⁵ series the blood specimens up to nineteen different ones from one patient were sent to Lowenstein without diagnosis. It is believed that the irregularity of the showers of bacilli appearing in the blood is responsible for the inconstant findings. However with or without confirmation ⁷⁶¹ of all of Lowenstein's findings the frequent occurrence of tubercle bacilli in the blood of patients with skin tuberculosis is a fact ⁵ 6 116 75 759.

⁷⁴⁶Stuempke G. Skin Tuberculosis Causes of Death. Arch f Dermat & Syph 193 216 222 1947

⁷⁴⁷Orlesbach R. Hautkrankheiten bei der Lungentuberkulose mit besonderer Berücksichtigung der Akne. Ztschr f Tuberk 67 405-416 1930

⁷⁴⁸Szántó J. Skin Disease in Pulmonary Tuberculosis. Dermatologica 38 17-48 1943

⁷⁴⁹Gáll G. Clinical Types of Pulmonary Tuberculosis Associated With Skin Tuberculosis. Tuberkulózis 1 253 59 278 779 (Hungarian with English summary) Zbl 47 150

⁷⁵⁰Meje J. Tuberculosis als Organsystemerkrankung. Acta tuberc Scandinav 9 67 283 1935 Zbl 11 569

⁷⁵¹Kolle W and Küster H. Tuberkelbacillen im strömenden Blute. Deutsche med Wchnschr 1934 I 309 313

⁷⁵²Rubin E H. Hematogenous Tuberculosis in Adult. Generalized Hematogenous Tuberculosis. Am Rev Tuberc 39 557 546 1939

⁷⁵³Wilson O B. Tuberculous Bacillæmia. Medical Research Council Special Report Series No 187 London 1933

⁷⁵⁴Mathies M A E. Resultate mit der Lowenstein'schen Blutkulturmethode bei verschiedenen Formen der Hauttuberkulose. Wien klin Wchnschr 45 719 720 1932

⁷⁵⁵Iibuchi T. Züchtung von Tuberkelbacillen aus strömendem Blut. Schw W med Wchnschr 1933 I 307-310

⁷⁵⁶Popper H, Bodart F and Schindler W. Tuberkelbacillenzüchtung aus Blut. II. Virchows Arch f path Anat 236 615-637 1932

⁷⁵⁷Courmont P, Osté J and Micheli J. Bacillémie tuberculeuse et tuberculose cutanée. Presse méd 42 497-498 1934

⁷⁵⁸Oro A. Sul valore di tutto Lowenstein per lo studio della bacillæmia nella tubercolosi cutanea e nella tubercolosi. Arch Ital di dermat 33 3 15 1937

⁷⁵⁹Lowenstein E. Tuberculous Bacillæmia and Its Significance in Medicine. Quart Bull Health Organ League of Nations 4 619-632 1935

The start of cutaneous tuberculosis in the intima of veins was demonstrated a long time ago⁷⁵ The distribution of the lesions in the cases of post exanthematic lupus⁷⁶ hardly allows any other explanation than general spread by the circulation with selective 'take' in some sites and failure to take in others (see chapter on hematogenous skin infection)

Blood borne infection may lead to all of the well known pictures of skin tuberculosis While hematogenous infection is the cause of the papulonecrotic and indurative types of tuberculosis and of the majority of the lupus vulgaris cases it is much less common in scrofuloderma and only few instances have become known in tuberculosis verrucosa cutis

Cutaneous Tuberculosis

The primary lesion of *lupus vulgaris* regardless whether of endogenous or ectogenous origin is the *lupus nodule* as it is called though it is usually only a *macule* In its early and uncomplicated stage this is a pinhead to lentil sized red or copper colored smooth spot Under glass pressure the spot does not fade and the blanching of the surrounding skin makes it stand out more clearly in a red brownish or dark yellow color In suitable light it is strikingly trans

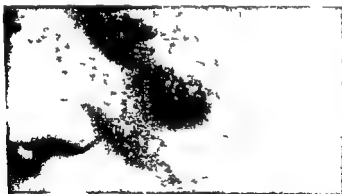


Fig. 95 — *Lupus vulgaris* (tumidus) (Courtesy Dr. M. J. J. J. J.)

parent which is responsible for the often used comparison with apple butter If one gently tries to penetrate the surface with a fine bulbous probe one is surprised how easily the instrument sinks into the soft tissue at a degree of pressure which would not be sufficient to pierce normal skin Such early lupus nodules are most commonly seen on the face particularly on and around the nose The great variety of pictures which may be encountered during the course of lupus vulgaris can be explained by a number of factors the dominant role of any one being able to create a clinical variety Increase in number and coalescence of the spots may lead to extremely chronic patches of flat lupus which may be as small as a pin or cover entire regions Such large flat lesions

⁷⁶Artom M. Tuberculosis cutis ex post morbillis Arch Ital di dermat 2 2 3 23 1933

48 per cent ⁷⁴⁶ From these and many other statistics it can be concluded that the incidence of lung tuberculosis in lupus is a high one. On the other hand the percentages of skin tuberculosis in very large groups of tuberculous patients has always been found low 0.2 per cent ⁷⁴⁷ 1 per cent in 27 540 cases ⁷⁴⁸ less than 2 per cent in 18 000 cases ⁷⁴⁹. This compares well with many older statistics ⁷⁵⁰ and seems to bear out the old rule that lupus patients often become consumptive but that consumptives rarely develop lupus. While the figures seem to be very low the incidence of skin tuberculosis is still about 2 to 3 times higher in patients with pulmonary tuberculosis than in a comparable normal group. Similar tendencies as in the relationship of lupus and pulmonary disease prevail in its relation to surgical tuberculosis. Among 275 lupus cases were 16 per cent with bone or joint tuberculosis while among 371 cases with tuberculosis of the bones and joints only 5 per cent had lupus ⁷⁵¹. The isolation of tubercle bacilli from the blood either by animal inoculation or by culture with the Lowenstein method has recently been more often successful than was held possible before. It is true that many observers could not obtain the same results as Lowenstein ⁷⁵². The positive findings however carry more weight than the negative ones. Kren ⁷⁵³ could show that if blood culture of patients with lupus vulgaris erythema induratum and lupus erythematosus was done more than seven times positive cultures could be found in all cases. The frequently negative blood cultures are most likely due to technical difficulties to unfavorable time of testing and to the too small numbers of the investigations. In Kren's ⁷⁵⁴ series the blood specimens up to nineteen different ones from one patient were sent to Lowenstein without diagnosis. It is believed that the irregularity of the showers of bacilli appearing in the blood is responsible for the inconstant findings. However with or without confirmation ⁷⁵⁵ of all of Lowenstein's findings the frequent occurrence of tubercle bacilli in the blood of patients with skin tuberculosis is a fact. 5 25 116 75 759

⁷⁴⁶Stuempke G. Skin Tuberculosis Causes of Death. Arch f Dermat & Syph 193 216 2 2 1942

⁷⁴⁷Orlesbach R. Hautkrankheiten bei der Lungentuberkulose mit besonderer Berücksichtigung der Akne. Ztschr f Tuberk 87 405-416 1930

⁷⁴⁸Antó J. Skin Disease in Pulmonary Tuberculosis. Dermatologica 88 17-48 1943

⁷⁴⁹Gáli G. Clinical Types of Pulmonary Tuberculosis Associated With Skin Tuberculosis. Tuberkulózis 1 253 259 78 279 (Hungarian with German summary) Zbl 47 9

⁷⁵⁰Meyr J. Tuberkulose als Organpatenerkrankung. Acta tuberc Scand 9 67 98 1935 Zbl III 569

⁷⁵¹Kohl W. and Küster E. Tuberkelbacillen im strömenden Blute. Deutsche med Wch schr 1934 I 309-313

⁷⁵²Rubin H. Hematogenous Tuberculosis in Adult. Generalized Hematogenous Tuberculosis. Am Rev Tub c 39 557 586 1939

⁷⁵³Wilson G. Tuberculous Bacteraemia. Medical Research Council Special Report Series No 182 London 1933

⁷⁵⁴Mathiesen A. W. Resultate mit der Lowensteinischen Blutkulturmethod bei verschiedenen Formen der Hauttuberkulose. Wien klin Wchnsch 46 719 720 1932

⁷⁵⁵Ibbuchi T. Züchtung von Tuberkelbacillen aus strömendem Blut. Schweiz med Wchnsch 1933 I 307-310

⁷⁵⁶Popper H. Bodart W. and Schindler W. Tuberkelbacillenzüchtung aus dem Blute II. Virchows Arch f path Anat 236 615-637 1932

⁷⁵⁷Courmont P. Gaté J. and Michel P. J. Bacillémie tuberculeuse et tuberculose cutanée. Press méd 42 407-498 1934

⁷⁵⁸Oro A. Sul valore del metodo Lowenstein per lo studio della bacillemia nella tubercolosi cutanea e nelle tubercolidi. Arch Ital di dermat 12 3 15 1937

⁷⁵⁹Lowenstein H. Tuberculous Bacteraemia and Its Significance in Medicine. Quart Bull Health Organ League of Nations 4 819 832 1935

Fig 97



Fig 98

FIG 97 — Lupus vulgaris involving the earlobe. Exceedingly chronic course; not worn off ear lob.

FIG 98 — Lupus vulgaris. A great malodorous halberd excised and the defect covered by full thickness skin transplantation. Recurrent lupus lesions did not invade the transplant. Still with lesions.

are often scaly so that they may resemble psoriasis this is still more likely if the outlines are circinate. The tuberculous tissue may grow above the skin level and form elevated hypertrophic and even fungating or tumorlike granulations. *Lupus hypertrophicus*, *lupus tumidus* and other terms describe this variety which usually involves the nose, the lips and the lobe of the ear.



Fig. 99.—Lupus vulgaris. (Courtesy Dr. M. Jensen.)

Ulceration and crust formation are more often a feature of the hypertrophic than of the flat forms. In the latter the ulceration is usually shallow and more marked along the edges. The healing tendency and scar formation vary, though healing is rarely complete. The lupus may spread with an active *serpiginous* edge over large areas, leaving in its wake a scar which usually contains some lupus nodules. Such annular or gyrate lesions may resemble syphilis or ringworm. The face may gradually become scarred, shrunken and immovable, and the conjunctiva and finally the eye itself may be destroyed. The mouth may be reduced to a small rigid hole. Such terminal stages may equal leprosy in dreadfulness. Cancer is not an uncommon complication. The suffering of such patients is beyond description. Such cases are fortunately rare, especially in America, but they can be seen in numbers in all the European lupus hospitals. This tragic outcome, however, is an exception. In the vast majority of the cases the lesions are stationary or slowly progressive and often

amenable to treatment. Recurrences are very common. Spontaneous regression occurs but is rarely complete.

The *histology* of the lupus nodule shows a conglomeration of typical tubercles with epithelioid cells, giant cells, lymphocytes and central necrosis, the latter often not particularly marked. The same factors which by their dominance decide the clinical picture also produce a great histological variety.



Fig. 100. Lupus vulgaris. (Courtesy Dr. Garrett Cooper.)

It is now almost generally accepted that *lupus is the expression of a cutaneous tuberculous superinfection with own or other tubercle bacilli*. Existing tuberculosis shapes a tuberculous infection of the skin into lupus, thus making it a *manifestation of an internal disease*. Lupus vulgaris starts in 50 per cent of the cases during the first two decades of life⁷⁶¹ a fact which is not easy to explain. Scrofuloderma and children's diseases like measles may play a part though convincing cases are not very common. The postexanthematic lupus is a good example of hemitogenous lupus⁷⁶². It is not too rarely seen to start shortly after or even during the measles and also after other acute exanthems. The postexanthematic lupus is often disseminated and appears simultaneously in several or many spots. Artom⁷⁶³ suggests that the energy during measles favors the development of postexanthematic lupus. The prognosis is relatively good since the seeded lesions usually remain inactive.⁷⁶²

⁷⁶¹Zieler, H. Primary Appearance of Chronic Skin Diseases at Various Ages With Special Reference to Lupus Tuberculosis. Arch. f. Dermat. u. Syph. 103: 23-30, 1941.

⁷⁶²Leiner, C. and Aptler, H. Über disseminierte Hauttuberkulosen im Kindesalter. Ergebn. d. inn. Med. 7, 1911.

⁷⁶³Artom, M. Über die Entstehung des Lupus vulgaris. Arch. f. Dermat. u. Syph. 103: 23-30, 1941.

Lupus miliaris disseminatus (Lupus follicularis Tilbury Fox 1878) is a follicular form of lupus which almost always affects the face only. It has a great similarity to acne and rosacea. In fact most cases go under these diagnoses for a long time. After an initial stage of erythema has passed follicular papules develop often with scales a yellow center erythema and subcutaneous nodules. The lesions are distributed over the nose the cheeks the chin and though less pronounced the forehead and other parts of the body. On close *diascopic inspection* the apparently pustular efflorescences show typical lupus tissue. The lesions appear in crops do not coalesce do not contain pus and have a marked healing tendency. The histological picture is that of typical tuberculosis. The distribution in the perifollicular vascular plexus and other histological findings prove the hematogenous character. Tubercle bacilli have rarely been found in the lesions. Pulmonary and other visceral tuberculosis has been found in a considerable number of the cases but the tuberculin reaction is often weak. The prognosis of the condition itself⁷⁴ is favorable and it responds well to peeling with strong ultraviolet light.

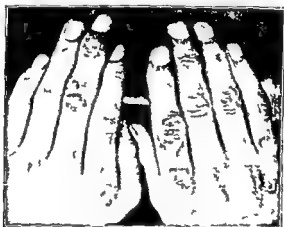


Fig. 101. Tuberculo verrucosa cutis. (Courtesy of the late Dr. W. A. Peck, from *Quintessence of the Diseases of the Skin*, The C. V. Mosby Company.)

Tuberculosis verrucosa cutis starts as a firm prominent nodule differing from lupus by the lack of transparency and the great resistance to the piercing probe. The papules increase peripherally coalesce but little become hyperkeratotic and later verrucous. Follicular abscesses are common especially in lesions which have reached more than coin size and greater thickness. The patches may reach great size. They are frequently seen over the bony prominences of the hands and feet. The right hand is most often affected⁷⁵. The knuckles and the ankle areas are affected only occasionally. The lesions are mostly single or few in number but hematogenous dissemination with many

⁷⁴Peck & M. *Lupus Miliaris disseminatus* *Arch. f. Dermat. u. Syph.* 188: 515. 1929

⁷⁵Ledermann & C. *Statistische Untersuchung über Tuberculosis verrucosa cutis* *Arch. f. Dermat. u. Syph.* 107: 163-169 1913

lesions has been seen. There is a decided preponderance of the male sex because the disease is often an occupational infection of slaughterhouse workers who are usually males but occasionally the disease also occurs in other persons who have contact with tuberculous material. The occupational character accounts for the common distribution on the hands and feet. It also occurs as an autogenous



Fig. 100.—Arophulid rima. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

superinfection with the sputum of patients with pulmonary tuberculosis. The bovine type of the tubercle bacillus has been found in 50 per cent or more of the cases, and bovine infection is probably responsible in all slaughterhouse cases.

Volk states that no explanation could be given why in one case tuberculosis verrucosa and in other cases lupus results from superinfection. Probably in spite of exceptions the terrain of the hands and feet which has a greater keratotic tendency than other parts is one of the influencing factors. This is illustrated

by cases of hematogenously disseminated skin tuberculosis with tuberculosis cutis verrucosa on the arms and lupus on the face.^{368, 39}

The close similarity of tuberculosis verrucosa cutis and some phases of blis tomycosis must be emphasized. Verrucous tuberculosis has a greater tendency to heal than lupus vulgaris and the response to treatment is more complete. The microscopic picture is that of tuberculosis but combined with parakeratosis and hyperkeratosis. Lymphangitis is a frequent complication.



Fig. 103 - Tuberculosis cutis colliquata (scrofuloderma). (Courtesy Dr. M. J. J. J. J.)

Tuberculosis colliquata (scrofuloderma) is a cold abscess of the skin, most frequently originating in a subcutaneous tuberculous focus, usually a lymph node or bone. It starts as a subcutaneous nodule which becomes adherent to the skin and forms an abscess or sinus without acute symptoms. Several such lesions may coalesce into a network of sinus abscesses, scars and ulcers, not infrequently surrounded by lupus. The most common site of scrofuloderma is the neck, with its great number of easily infected lymphatic nodes. Tuberculosis of the sternum and of the ribs are other starting points for colliquative tuberculosis of the skin. Children and young adults are most often affected. Scrofuloderma occurs occasionally, mostly in young children, in a hematogenous

distribution without connection with underlying structures. These cases closely resemble the corresponding phases of sporotrichosis, blastomycosis and coccidioidomycosis. The prognosis of scrofuloderma and the therapeutic response is usually good, though the process may last several years.

Ulcerati ■ tuberculous of the orifices in pulmonary or genitourinary tuberculosis produces characteristic lesions most often found on the tongue and around the anus but also on the lips, the ears and the glans penis. On the tongue the lesions may appear as shallow jagged oblong round or rhagadiform ulcers, the papular primary stage of which is seldom seen. The floor of the ulcer is granulated and yellowish, the edge slightly undermined. The lesion progresses by ■ coalescence with minute pustular lesions in the surroundings. There is little induration and sometimes surprisingly little, sometimes surprisingly, severe pain. Perianal ulcerative tuberculosis occurs in 5 to 10 per cent of patients with pulmonary tuberculosis. All abscesses and fistulae in such patients must be considered suspects. 76 768



Fig. 101.—Tuberculous ulcer of the tongue in pulmonary tuberculosis.

This ulcerative type of lesion contains more tubercle bacilli than the other forms. In line with this fact is the frequent absence of typical tubercular structure and the dominance of nonspecific inflammation. Ulcerative tuberculosis of the tongue is more frequently seen in men than in women.

Tuberculous ulcers of the orifices are important indicators of visceral, especially pulmonary, tuberculosis.⁴⁷⁻⁴⁹

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^{76c} 1 A u o y R a 1 M i l l i W T h e r e l o d o f t h T o g u R e p t o f T h r e e C a s e s J A M A
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Miliary tuberculosis of the skin is almost exclusively seen in infants and young children^{176 177}. In adults the miliary foci are numerous in the subcutis but do not reach the skin. The rash consists of pinhead sized hardly prominent often hemorrhagic and slightly umbilicated papules. These lesions are quite dense in some areas. They may heal spontaneously leaving a slightly depressed pigmented spot. The exanthem is inconspicuous and may easily be overlooked¹⁶². The diagnosis is rarely made without biopsy. The histologic structure is not so much tuberculoid as inflammatory in character. There are tremendous numbers of bacilli. Small vessels are sometimes solidly packed with bacillary emboli¹⁷⁶ and surrounded by necrosis but there is a vast disproportion between the number of bacilli and tissue defense⁷. The tuberculin reaction is sometimes negative¹⁷⁸. Hoyle and Vazeey¹⁷⁹ list about 16 per cent tuberculous skin manifestations in their series of 120 cases of miliary tuberculosis. The prognosis is hopeless.

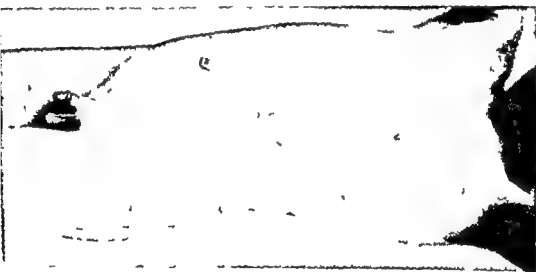


Fig. 100.—*Lichen scrofulaceus* (Courtesy Dr. Fritz Urbach)

In *tuberculosis lichenoides* or *lichen scrofulaceus* large numbers of micro papular mostly follicular often conical and keratotic skin colored or pink to yellowish brown lesions are grouped in round oblong or irregular patches. They are mostly found on the back particularly in the lumbosacral region and on the abdomen. The lesions develop slowly and patches may persist for years. Older lesions often have a scale and if they are packed very closely together in old plaques a large desquamating surface may give a

- ¹⁷⁶ G. Igel, P. Die Beteiligung der Haut bei Miliartuberkulose. Virchows Arch f. path. Anat.
284: 531-603, 1903.
¹⁷⁷ Koch, H. Die Tuberkulose des Säuglingsalters. Erg. f. inn. Med. u. Kinderh. 24: 70-94.
191.
¹⁷⁸ Volk, R. Hamatogene multiple subcutane tuberkulöse Abszesse. J. 41: 69.
¹⁷⁹ Noel, H. Tuberculosis utis miltaris acuta generalisata im Kindesalter. Jahrb. f. Kinderh. 131: 24-28, 1911.
¹⁸⁰ Hoyle and Vazeey. Chronic Miliary Tuberculosis. London, 1913. Oxford University Press.

psoriasisform appearance. Usually the center of such plaques is less scaly than the edges but more grater or chagreen leather like. In some cases some or all of the papules bear a hard sharp horny little spine. The microscopic picture shows almost invariably tuberculoid structures without or with very few bacilli.



Fig. 111. Papilloneroth tuberculoid. Courtesy Division of Dermatology, Department of Medicine, University of Chicago.

Phlyctenular conjunctivitis is a frequent accompaniment. The dermatosis is of great⁷⁴ symptomatic significance. It indicates almost always the existence of internal tuberculosis usually of a more benign type. The dermatome is rare in adults more common in children. It frequently makes its appearance after measles and other acute infections. However there are great geographic differences. Tuberculosis cutis lichenoides is a common sight in the European skin clinics while in North America and particularly in the tropics and subtropics it is like all types of skin tuberculosis either rare or nonexistent⁷⁵ 77 (Pu e y after Volk⁷⁶)

Tuberculosis papulon croatica. This variety of cutaneous hematogenous tuberculosis has been described under a score of names⁷⁶ 78 among which the odd terms follicul and acnitis are still being used because they were given by the first describer T. Barthélemy. The term tuberculid is also often applied.

The evolution of the lesion is simple and characteristic. A cutaneous nodule of linseed size grows within about four weeks to its maximal size which does not exceed that of a cherry stone and becomes a movable firm well defined slightly raised dusky bluish red or brown papule. The center of the fully developed papule shows a yellow head which however does not contain pus as one might expect but a rather tough necrotic core which may come out by itself leaving a small punched out ulcer. More often a deep necrotic scab is formed which comes off after two to four weeks producing a small crater shaped scar with sharp steep pigmented edges. The scars are often more characteristic than the active lesions. Papulonecrotic tuberculosis is usually fairly evenly disseminated over the arms hands and legs and occasionally the trunk. The extensor surfaces the skin about the joints and the buttocks are more often affected but no area is immune.

Genital lesions may suggest secondary syphilis⁷⁷. Barthélemy called acnitis a deeper situated acneiform papulonecrotic tuberculosis of the face. This condition is closely related to lupus miliaris faciei. The lesions of papulonecrotic tuberculosis appear in crops and have a much more marked spontaneous healing tendency than other forms of skin tuberculosis. This type of skin tuberculosis is less responsive to tuberculin than is lupus⁷⁸. The microscopic structure is tuberculoid. Tubercle bacilli are scarce but have quite often been found particularly in children.⁸

Combination with pulmonary and other forms of tuberculosis including skin tuberculo is is the rule.

Tuberculosis indurata (Erythema induratum Bazin's disease) is a rather rare dermatosis characterized by cutaneous or subcutaneous nodules or plaques of much larger size than in the papulonecrotic lesions. There are usually only a few lesions scattered over both legs especially the calves and rarely also over the posterior aspects of the thighs the buttocks the forearms or the face. They start as indolent nodules which grow within several weeks to almond or even

⁷⁴Gahan F Incidence of Tuberculosis of the Skin Arch Dermat & Syph 48 130-134 1942

⁷⁵Barthélemy & R L & J M T Barthélemy Arch Dermat-syphil Hôp St Louis 9 79

⁷⁶Mirra J S superficial papulonecrotic Tuberculid in Negro Arch Dermat & Syph 47 6

636 1943

palm size. Such fully developed lesions are visible as a pink or livender smooth erythema resembling the lilac ring of scleroderma. Palpation reveals an indurated plaque of varying depth which is sometimes connected with cordlike phlebitic changes. The infiltrate is movable with the skin and usually is not tender. In larger lesions the center is depressed or it may though rarely become ulcerated and then resemble a syphilitic gumma. The plaques heal spon-



Fig 108



Fig 109

Fig 108 -Tuberculous induration (erythema induratum) (Courtesy Dr. M. Jeaner)

Fig 109 -Tuberculous induration (erythema induratum) (Courtesy Dr. M. Jeaner)

taneously but the course may take many weeks, months, or even years if ulceration occurs. The oral mucosa is occasionally involved.^{773, 779} The dermatome is many times more common in the female than in the male sex. New crops are usually observed during the winter and spring.⁷⁷⁹ The tuberculin reaction is strongly positive. Tubercle bacilli are rarely found in the lesions. The struc-

⁷⁷³Schliachl J. Erythema induratum. Arch f Dermat & Syph 90: 371, 1904.

⁷⁷⁹Forster A. Erythema induratum. Arch f Dermat & Syph 153: 99, 1917.

ture is decidedly tuberculoid. Combination with visceral tuberculosis and with other forms of cutaneous tuberculosis is not rare.³⁶⁶

Rosacea like Tuberculosis Lewandowsky⁷⁸⁰ described this form of skin tuberculosis which in the majority of cases is seen in women^{723 781 78} of 30 to 60 years of age. The disorder develops gradually. The typical case shows a great number of papules, mostly follicular, scattered symmetrically over the cheeks and forehead often leaving the nose and chin free. The papules are small to medium sized with a decided yellowish brown tinge and do not completely



Fig. 110 — Rosacea like tuberculosis (Lewandowsky). Note spots which become more distinct under glass pressure. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

fade under the pressure of glass. The diascope does not, however, show the transparent apple jelly colored lupus nodule as in lupus miliaris which it resembles. There may be some pustulation, cyanotic erythema and a certain amount of telangiectasis, but not as marked as in rosacea. Scaling is sometimes present.^{368 782}

⁷⁸⁰ Lewandowsky, W.: Rosacea ähnlich Tuberculide des Gesichts. Co. Bl. Schweiz. Ärzte 47: 150, 1917.

⁷⁸¹ Warren, L. J. and Crawford, F. H.: Rosacea like Tuberculosis (3 Cases). Arch. Dermat. & Syph. 31: 174, 189, 193.

⁷⁸² Nicholson, H. F. and Wilkins, L. H.: Tuberculoid macula of the face. Arch. Dermat. & Syph. 29: 260-269, 1934.

³⁶⁶ MacKee, E. M. and Sulzberg, M. B.: Rosacea like Tuberculosis of Lewandowsky. Arch. Dermat. & Syph. 33: 159-163, 1935.

The microscopic structure is tuberculoid. No bacilli seem to have been found in the lesions so far. The patients are usually though not always ⁷⁸¹ highly sensitive to tuberculin which is in contrast to the reaction in lupus miliaris. Visceral or other cutaneous tuberculosis mostly of benign character was found in a fraction of the cases. Though still rare rosacea like tuberculosis is a relatively frequent form in America ^{7 5}.

found tubercle bacilli in the lesions in 3 adults and 3 children. These authors were unable to detect any pulmonary changes.

The *tuberculin reactions* in children and young adults were positive in over 90 per cent and more strongly positive than in control groups.⁷⁹ There are series of many hundreds of observations available.^{783, 795} In a number of instances the test was known to have been negative before the outbreak of erythema nodosum and was observed to become positive.^{796, 799}

The *provocation* of erythema nodosum⁸⁰⁰ or at least of new lesions by tuberculin tests has been reported by Kropitchev and Verzner,⁸⁰¹ Wallgren,⁸⁰ saw erythema nodosum after Calmette Guérin vaccination. Yet it should be emphasized that in large series⁷⁹⁵ 3 to 8 per cent of the cases have been definitely declared tuberculin negative.

Simultaneous manifestations of tuberculosis have been discovered in many instances. Prag⁷⁹³ saw roentgenologic pulmonary changes in 91 per cent of his 157 cases; other authors in about 50 per cent.^{794, 801, 806} Few writers found the lungs involved in only a minority of their⁸⁰⁷ cases.⁸⁰⁸

The pulmonary involvement was usually interpreted as recent or primary.⁷⁹¹

A dense and enlarged hilus, tracheobronchial lymphadenopathy, peribronchial infiltration, pleural exudate or frank hyperplastic tuberculosis are the usual findings. The lymph node enlargement was more often bilateral than unilateral and the pulmonary infiltration was unilateral in about 50 per cent of the affected cases.⁸⁰⁹ The relatively benign character of the hilar reaction is sometimes shown by its complete disappearance in a short time.⁸⁰⁷

- ⁷⁹²Rotnes P. L. Erythema Nodosum in the Adult. Nord med tidskr. **11**: 791-99, 1937. Zbl. **111**: 453.
- ⁷⁹³Prag A. R. Erythema nodosum. Hygi. a Stockholm **24**: 9-601, 1937. Zbl. **111**: 164.
- ⁷⁹⁴Giersten C. 93 Cases of Erythema Nodosum. Acta med. Scandinav. **82**: 87-110, 1934. Zbl. **109**: 346.
- ⁷⁹⁵Landorf N. Tuberculin-negative Erythema nodosum. Acta paediat. **17**: 180-187, 1935. Zbl. **108**: 438.
- ⁷⁹⁶Comby J. A propos de l'érythème noueux. Bull. et mém. Soc. méd. d. hôp. de Paris **80**: 1740-1747, 1934. **52**: 973-978, 1937.
- ⁷⁹⁷Stavropoulos J. Quelques considérations sur le cas d'érythème noueux. Bull. Soc. pédiat. de Paris **23**: 585-90, 1935.
- ⁷⁹⁸Bethou E. and Berthet F. Un cas de primo-infection tuberculeuse avec érythème noueux chez une fillette de onze ans. Bull. et mém. Soc. méd. d. hôp. de Paris **111**: 503-510, 1935.
- ⁷⁹⁹Ontaneda L. E. Rossi J. E. A. and Lasquallini R. Q. Erythema Nodosum as a Symptom of First Tuberculous Infection in Adult. Rev. Assoc. méd. arg. **49**: 915-9, 1933. Zbl. **86**: 362.
- ⁸⁰⁰Lafose P. Erythème noueux chez un cas tuberculeux après des injections de tuberculin. Rev. de la tuberculose **1**: 461-467, 1935.
- ⁸⁰¹Kropatchev A. D. and Verzner V. V. Erythema Nodosum in Small Children. Sov. t. pediat. **12**: 57-65, 1936. Zbl. **66**: 59.
- ⁸⁰²Wallgren A. Erythema nodosum nach Calmette-Impfung. Skand. tidn. pp. 1303-1305, 1932. Zbl. **100**: 300.
- ⁸⁰³Stallé S. Erythema Nodosum. Szepiaki arch. za w. lek. **35**: 146-163, 1937. Zbl. **111**: 39.
- ⁸⁰⁴Giersten C. Four Cases of Erythema Nodosum and Prühl's filtrat. Acta med. Scandinav. **82**: 55-66, 1934. Zbl. **111**: 347.
- ⁸⁰⁵Hamburg Z. Ulin E. and Kropatchev A. Etiology of Erythema Nodosum in Children. Borba s. tuberk. **11**: 119-115, 1931. Zbl. **80**: 641.
- ⁸⁰⁶Saxl O. Beitrag zur Ätiologie des Erythema nodosum. Arch. f. Klin. **11**: 92, 95-301, 1931.
- ⁸⁰⁷Paul L. W. and Pohl E. A. Erythema Nodosum. Medical and Pulmonary Changes. Radiology **27**: 131-137, 1941.
- ⁸⁰⁸Pink W. W. Pathogenesis of Erythema Nodosum With Special Reference to Tuberculosis reprotoecic Infection and Rheumatic Fever. Arch. Int. Med. **59**: 65-81, 1937.
- ⁸⁰⁹Kerley P. The Etiology of Erythema Nodosum. Brit. J. Radiol. **11**: 204, 1947.



Fig 111—Erythema nodosum



Fig 112 Erythema nodosum. Left: marked enlargement of the mediastinum and hila lymph nodes. Right: four weeks later. There was no demonstrable associated pulmonary disease. (From Joppet and McNamee, *New England J Med*.)

The lung changes have quite frequently been interpreted as a primary complex.³⁰⁴ This is in line with the fact that fresh pulmonary changes are mostly encountered in young individuals. It is of special interest that young adults who by their negative tuberculin tests show that they have so far escaped tuberculous infection are more likely to get erythema nodosum on exposure to tuberculous infection than are controls. These persons usually become tuberculin positive in the course of the disease. This has been demonstrated in student nurses³¹⁰ and newly inducted soldiers.³¹¹ Such and similar cases³¹ carry much weight against the argument that a positive tuberculin reaction does not necessarily have to be related to erythema nodosum.⁷⁸⁴ If it is true that erythema nodosum is rare in lung sanitariums this could be explained by the fact that most cases in these institutions are no longer in the early stages. Erythema nodosum has been seen to appear in the presence of extrapulmonary tuberculosis e.g. a cold abscess of the neck,³¹³ or of the breast³¹⁴ or after the surgical severing of pleural adhesions.³¹⁵

Tubercle bacilli in the blood of patients with erythema nodosum have been demonstrated quite frequently.^{757 816 819} (12.5 per cent Sienz and Broca after Milian and Brodier⁷⁸⁸ L. Neckám Jr.⁸²⁰ in a case of so called typhobacillosis). They do not prove conclusively the tuberculous etiology of the skin lesion since bacillemia is frequent in tuberculosis but they are a valuable support of a hemato-genous pathogenesis.

Tubercle bacilli have been demonstrated in the gastric juice especially of children with erythema nodosum^{790 813 81} and also in the urine (Ramel after Milian and Brodier⁷⁸⁸). To these findings applies what has been said of the etiologic value of the bacillemia.

³¹⁰Punch A. L. Erythema Nodosum. Etiology. Lancet 2 10 11 1941.

³¹¹Tornell F. Untersuchung von Knoten erythemfällen und ihrer Umgebung in der Literatur. 1 11 Sv Nat Tuberk Kvskr 80 3 12 1935 Zbl 82 176.

³¹²Debré M. R. Erythème noueux et tuberculose. Bull Soc franç de dermat et syph 48 11 1091 1096 1938.

³¹³Gordon H. Case of Tuberculous Infection With Erythema Nodosum. Brit J Dermat 45 60 71 1933.

³¹⁴Penry W. M. Erythema Nodosum. Brit J M 2 148 1931.

³¹⁵Colette and Bernard J. Erythème noueux (typhé) après ecto- et trichozun tuberculeuse. Bull et mém Soc méd d Hôp d Pa 18 80 1640 1697 1934.

³¹⁶Stamm H. Tuberkelbakterien im Blut bei Erythema nodosum (negativer Intrakut. Tuberkulose und Erythema Nodosum). Verhandl schwed naturf Gesellsch p 44 193.

³¹⁷Faisan H. Oumansky V. a. Lucas P. Erythème noueux et tuberculose. Bull Soc pédiat de Paris 28 4 3 554 1930.

³¹⁸Naranjo F. Ueber Tuberkelbacillen bei Erythema nodosum in Kindesalter. Ztschr f Tuberk 71 11 16 1934.

³¹⁹Boa F. Erythema Nodosum mit Tuberkelbakterien im Blut. Hospitalwrt 76 884 893 1933.

³²⁰Neckám Jr. L. Fall von Lanlousyecher Typhobacillose und Erythema nodosum. Klin Wchnschr 13 1944 1466 1934.

³²¹Gofstoe V. Pathogenese des Erythema nodosum. Monatsschr f Kinder 61 219 67 1935.

³²²Wall. Erythema Nodosum bei Kindern. Nord med tidkr 2 493-493 1931.

³²³Hilli. of Tubercle bacilli in the Gastric Juice from 100 Cases of Erythema Nodosum. Cases of E. at 13 397-399 193.

While the prognosis of the dermatosis itself is good *severe and even fatal tuberculosis* has in a minority of the cases been seen (27 per cent ⁷⁹ 12 per cent ⁸⁴ 14 per cent ⁸⁵) to follow erythema nodosum

Tuberculous meningitis ⁷⁹⁶ ⁸⁶ ⁸⁷ miliary tuberculosis and florid pulmonary phthisis ⁸²⁰ have been reported occasionally. The most experienced observers agree that every case of erythema nodosum should be watched until the return of normal temperature and normal sedimentation rate.

The Scandinavian writers have often emphasized the *public health* aspect of erythema nodosum ⁸¹¹ ⁸¹² ⁸¹³. They regard erythema nodosum especially in school children as an indicator of an open source of tuberculosis in the surroundings. A school mate ⁸²³ a family member or a coworker has time and again been found to spread tubercle bacilli which may account for the tuberculous infection by which erythema nodosum seems to be caused. After erythema nodosum children should remain in bed for several weeks and should be kept from school until all danger of acute tuberculosis can be safely disregarded ⁸¹⁴.

Small *epidemics* of erythema nodosum in hospital wards boarding school and families ⁸²⁶ have been observed several times and the source of the tuberculous infection has often been found ⁸²⁶ ⁸²⁷.

After the remarkable evidence which has been produced particularly by the Scandinavian authors it must be accepted that a varying and often large portion of the erythema nodosum eruptions is due to tuberculosis in the early stages particularly in juvenile at the time of the development of skin allergy ⁸²⁸. The allergic pathogene is finds fresh support in the parallel and more clear cut cases of erythema nodosum in coccidioidomycosis (which see). Here the conditions are less complicated because most of the patients have never been infected and do not come from infected surroundings. In coccidioidomycosis the ery-

⁷⁹ Lesclapart F, Bojarski A, a l'Callat P. L'procti clisé d'erythème noueux Arch d m d n f 38 1-30 1933

⁸⁰ Eckerström G. Erythema nodosum und Pleuritis. Ueber die Entstehung der Lungentuberkulose. Acta tuberc sc din 6 74-99 1933

⁸¹ Stokes J H. Erythema nodosum and Tuberculosis. Arch Dermat & Syph 3 23-31 1911

⁸² Mörbitz H. V. Maligne Raktik bei Erythema nodosum. Monat chr 11 Ind rh 67 9 1936

⁸³ Skalmowski T. Aetiology des Erythema nodosum. I. Klin d r. I. Stat pol ka 12 416-419 1933

⁸⁴ Lesclapart F. L'erythème noueux chez l'enfant. Bull Soc fra ç d dermat t yph 46 11 1057 1059 1035

⁸⁵ Couch G. Erythema nodosum und miliary. Spitalabtl für g Mo alchr 11 Klin rh 1933

⁸⁶ Ernberg H. Das Knotenerythem als Wärmegewebe. Nat Tub rk J vkr 30 13 1933

⁸⁷ Land M A. Multiple cases of Erythema nodosum in a Class of School Children. Arch Dis Child hood 7 1932

⁸⁸ Banjo I, Hiruma R, Fujita W H. Erythema nodosum and Tuberculosis. Canad J Pub Health 28 37-41 1934

⁸⁹ Ernberg H. Erythema nodosum. Nord med tidskr 4 30-236 1933 711 42 717

⁹⁰ Ellis A. Tubercular Etiology of Erythema nodosum. J v a g i t d rmatol 11 1933

⁹¹ Lefebvre A. Erythema nodosum. F yth ma nodosum. Bull Soc fra ç d dermat t yph 43 11 1096-1100 1933

⁹² Coudré A. Erythema nodosum et miliary. Leur apparition fréquente au moment de la primo-infection tuberculeuse. Bull t m f m Soc mé d H p d Paris 47 98 1931

⁹³ Lefebvre A. Erythema nodosum. Faits étiologiques et cliniques. Bull Soc fra ç d dermat t yph 43 11 1096-1100 1933

thema nodosum appears after the primary lung infection has produced allergy. The term "autogenous tuberculin reaction" ³³⁹ well expresses the pathogenetic theory. Some authors call erythema nodosum the exanthem of tuberculosis. This too regards the eruption in the light of the general observation that the beginning of the secondary phase of an infectious disease is often marked by an exanthem. The histologic findings sometimes show tubercloid structure but more often nonspecific inflammation especially around the veins. The lack of eosinophiles is an argument against an allergic pathogenesis. ³⁴⁰ The scarcity or the lack of tubercle bacilli in the lesions cannot be used as an argument against a tuberculous etiology since it may be explained by the strong defense which has developed and for which the positive tuberculin tests are proof. While especially in children and in cooler climates the important part which tubercle plays seems certain it needs to be emphasized that erythema nodosum has been seen in a great number of other infections ³⁴¹ e.g. *ulcus molle*, *lymphogranuloma inguinale*, *Boeck's sarcoid*, *coccidioidomycosis*, *trichophytosis*, *ulcus vulvae acutum* (Popoff 1938 after Pautrier³⁴¹) (Samek and Fischer after Pautrier and Woringer³⁴¹), *sypilis*, *leprosy*, *measles* and *rheumatic fever* as well as a drug eruption and finally without any apparent cause. The knowledge of the varied etiology of erythema nodosum invalidates an argument against a purely tuberculous etiology namely the cases which are numerous in some series in which by no method even by autopsy in some instances could tuberculous infection be found ³⁴²

The variations in the eruptions are remarkable. Poppel and Melamed³⁴³ found in a New York series only 4 out of 88 cases associated with tuberculosis. Ramel³⁴⁴ believes that idiopathic erythema nodosum is always in the child as well as in the adult the cutaneous manifestation of a tuberculous bacillemin. It seems best to regard erythema nodosum as a *clinical* rather than an *etiological* entity, however the important role of tubercle is especially in children cannot be denied.

Erythema exudativum multiforme has been suggested to be caused by hematogenous tuberculous infection ^{345 346}. English investigators^{346 347} were unable to duplicate the guinea pig inoculations. The idea cannot be considered established except possibly for some cases of the Landouzy type of tuberculous

³³⁹ Ernberg H. Erythema Nodosum and Tuberculosis. *Am J Dis Child* 46: 129-130, 1933.

³⁴⁰ Crzybowki F. Erythema Nodosum. *Bull Soc franç le dermat et syph* 45: 111-110, 3, 1936, 1934.

³⁴¹ Pautrier L. M. Ulmo A. and Baumit M. Erythema nodosum au cours d diverses infections. *Bull Soc franç de dermat et syph* 45: 111-110, 1, 1934.

³⁴² Lautrier L. M. Woringer F. and Zerni L. Erythema papulux infect. *Bull Soc franç dermat et syph* 40: 1-5-1-8, 1933.

³⁴³ Poppel M. H. and Melamed A. M. Erythema Nodosum. *N w E glanz J Med* 227: 3-5-330, 1942.

³⁴⁴ Ramel F. Erythema exudativum multiforme. *R pp Congr Dermatologistes La que franç pp* 59-194, 1933.

³⁴⁵ Dufour A. Erythema exudativum multiforme avec érythème polymorphe. *Icon mfd* 1930: 1-89-97.

³⁴⁶ Percival C. B. and Gibson H. E. Etiology of Erythema Exudativum Multiforme. *Brit J Dermat* 23: 379-381, 1931.

³⁴⁷ Hallam R. and Edington J. W. Investigation of Alleged Tuberculous Etiology of Erythema Exudativum Multiforme (Erythema). *Brit J Dermat* 23: 133-141, 1933.

bacillema⁸⁴⁸ Erythema multiforme and other exanthematic erythemas have been seen in association with erythema nodosum (Debre after Milian and Brodier⁷⁸⁸)



Fig. 113.—Erythema multiforme with typical erythema nodosum on the legs. To illustrate polyarthritides recurrent attacks in the same patient.

Initial Exanthema.—In infantile tuberculosis ephemeral and inconspicuous morbilliform roseolar urticarial or erythema multiforme like exanthems on the arms and legs have been observed occasionally by some authors and quite frequently by others. They may appear at the transition of the pre-allergic into the allergic phase of pulmonary tuberculosis^{849, 851} i.e. about two months

⁸⁴⁸ Near F. F. Cutaneous Tuberculosis and Central Medical Diagnosis. Ann. Int. Med. 8: 41-51, 1935.

⁸⁴⁹ Löffler (in F. A. Das Erstexanthem (Frühexanthem) der Kindheit. Tuberkuloseinfektion. Mon. ch. n. med. Wchnschr. 78: 535-537, 1927).

⁸⁵¹ von Möricz, D. Tuberkulotisches Frühexanthem. Wchnschr. 1934 II: 1091-1093.

⁸⁵² Kunzratz, H. Das Erstexanthem der Kindheit in Tuberkuloseinfektion. Wchnschr. 1934 I: 91-923.

after the infection. These exanthems being connected with the early allergic phases have been seen mostly in children. They are explained along the same lines as erythema nodosum.



Fig. 114.—Erythema exultans multiforum. (Courtesy Dr. M. J. Hurst.)

Lichen nitidus⁸⁵ consists of pinhead-sized glossy light-colored superficial papules which most often occur on the penile skin. The lesions develop slowly and without any characteristic changes. They may stay for years. The microscopic picture is that of an almost too typical tubercle just below the epidermis with many Langhans cells and little necrosis. In a number of cases coincident with pulmonary or cutaneous tuberculosis has been observed⁸⁶ but the tuberculous nature of the dermatosis is still controversial.

Granuloma annulare (Radcliffe-Crocker) is characterized by hard yellow-white almost flat papules arranged in coin-sized or larger rings most often on the dorsal of the hands rarely on the arms or elsewhere on the body. The course is slow and may become arrested at any stage. There are no complications or other changes than spontaneous regression sometimes after many years. The microscopic picture shows a deep-seated granuloma with central necrosis rarely⁸⁷ with a marked tuberculoid structure.⁸⁸

⁸⁵Pinkey, F. C. J. J. u. k. scherf msk Haut eruption. Lich. nitid. Arch f. Dermat. u. Syph. 85 11 1901.

⁸⁶Ruch (caul msk Ann. 1. 211 11 401 12 4.

⁸⁷Jacobi F. C. uloma Ann. 1. 11a 11 1 11 u. Gk. 10 70-83 1911.

J Jodassohn⁸² and later his pupils (Martenstein and Knoll⁸³) were impressed by the frequently negative tuberculin reactions in granuloma annulare in spite of many facts which pointed toward a connection with tuberculosis. They felt that granuloma annulare should be grouped with other positive anergic tuberculous conditions especially Boeck's sarcoid; Michael⁸⁴ reviewed 86 cases from the literature and found a definitely lower percentage of positive reactions than is found in the population at large. Tubercle bacilli have only exceedingly seldom been found in the lesions⁸⁵ the guinea pig inoculations being just as unsuccessful as the microscopic examinations. Combinations with pulmonary and other tuberculosis has been seen only in 16 to 20 per cent.⁸⁶ Tuberculin has had a healing effect in a number of cases and has occasionally provoked lesions.⁸⁷ The strongest argument against a tuberculous etiology is furnished by a number of cases in early childhood without tuberculosis and with negative tuberculin reactions.^{88, 89} Granuloma annulare is probably a clinical reaction common to different agents of which the tubercle bacillus is only one. Some authors believe in a toxic etiology.⁹⁰

Boeck's Sarcoid (Benign Miliary Lupoid)

Boeck's sarcoid is a rare systemic disease involving predominantly the skin, the lungs and the bones.

The trouble usually starts insidiously and takes an extremely chronic and unusually benign course. The original description of Boeck distinguished three types characterized by small disseminated cutaneous nodules or papules by larger and more grouped nodules and by diffuse sometimes very extensive infiltrated plaque. With the greater number of cases published transitional and other varieties have become known and cases without skin involvement have been recognized. It is now believed that the skin participates only in about half of the cases (Voshein and Bonnevie after Leitner⁹¹).

The clinical feature which connects the nodosities of varying size and shape is the microscopic appearance of small yellowish spots which resemble lupus lesions but are smaller and less transparent. These lupoid spots which are responsible for the name benign miliary lupoid may coalesce into larger areas. The small nodules are usually numerous giving the impression of an exanthem while the large nodules occur in smaller numbers. The lesions which are present simultaneously are in various stages of development. In some the skin may still be of normal color while in others definite lupoid red or brownish discoloration

⁸² Jodassohn hn J. Sarcoid und Lupus per lo. Korr. III 5 hn 12. Archiv 44 1474 1477 1914

⁸³ Martenstein J. J. K. Histology of Granuloma Annulare. With special reference to the Tuberculous Theory. Arch. Derm. Syph. 28 1 9-107 1913

⁸⁴ Michael F. R. Histology of Tuberculosis and Granuloma Annulare. Dermatologia 23 1-6-10 1914

⁸⁵ Voshein F. J. A. S. The suggested Tuberculosis Origin of Granuloma Annulare. Brit. J. Derm. 41 6-68 1914

⁸⁶ Jodassohn J. A. S. Histology of Granuloma Annulare. Bull. Soc. franc. d. dermat. et syph. 38 61 1911

⁸⁷ H. H. H. F. O. A. S. Granuloma Annulare. Brit. J. Dermat. 47 310 340 1913

⁹¹ Leitner A. J. D. Medizin. Bericht über Boeck'sche Krankheit. Basel 1914. Bernardschwer



Fig 115 — Boeck's sarcoid. Ring-shaped lesion with atrophic center. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)



Fig 116 — Boeck's sarcoid. Lupuli appear venous at pressure. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

tion has already developed. On the face such mature efflorescences are often bluish red with a yellow border. Other nodules may be regressing leaving a depressed atrophic scaly scar in the center while the periphery is still active red or brown sometimes telangiectatic and infiltrated. Such ring shaped or circinate figures surrounding a thin scar are particularly characteristic on the forehead and other parts of the face. Other typical though less common sites are the shoulders and the extensor surfaces of the arms occasionally the hands and feet where the ring form is usually less marked because the center is more apt to stay pigmented. The scalp may also become affected. Ulceration does not occur.

The lungs are frequently affected in Boeck's sarcoid 720 803 809 933 The sarcoid lesions in the lungs are small and disseminated mainly over the middle and lower parts. A diffuse fibrosis with stringy rather dense shadows radiating from the hilus toward the periphery 720 is often noticeable. A diagnosis of Boeck's sarcoid based on the lung picture alone is hardly possible. In cases without skin lesions a diagnosis of miliary or fibrotic tuberculosis or of carcinomatous or of less specific changes will probably be considered. A characteristic of the pulmonary changes is the chronic course and the fibrotic tendency, which is the analogy of the carrying of the skin lesions. In spite of widespread and dense changes of the lung the symptoms are usually only slight.

This is also true of the bone involvement³⁶⁹ Nielsen³⁶⁷ has observed 42 cases of Boeck's sarcoid over many years. He and many other authors find the small bones especially the terminal phalanges most commonly affected. Sarcoid pneumonia may precede the bone disease^{370 371}. The course is of course and complete regression of lesions could be demonstrated. The lesions are round embolic foci of granulation tissue which replace the bone and can be like a picture. Pathological fractures occur occasionally. If the bone is heavily affected the surrounding soft tissues may become swollen and give the picture of dictyitis or spinar ventosa. Bone lesions occasionally give rise to dermatomes occur in about 20 per cent of the cases³⁷². Similar lesions may

1. ¹ ² ³ ⁴ ⁵ ⁶ ⁷ ⁸ ⁹ ¹⁰ ¹¹ ¹² ¹³ ¹⁴ ¹⁵ ¹⁶ ¹⁷ ¹⁸ ¹⁹ ²⁰ ²¹ ²² ²³ ²⁴ ²⁵ ²⁶ ²⁷ ²⁸ ²⁹ ³⁰ ³¹ ³² ³³ ³⁴ ³⁵ ³⁶ ³⁷ ³⁸ ³⁹ ⁴⁰ ⁴¹ ⁴² ⁴³ ⁴⁴ ⁴⁵ ⁴⁶ ⁴⁷ ⁴⁸ ⁴⁹ ⁵⁰ ⁵¹ ⁵² ⁵³ ⁵⁴ ⁵⁵ ⁵⁶ ⁵⁷ ⁵⁸ ⁵⁹ ⁶⁰ ⁶¹ ⁶² ⁶³ ⁶⁴ ⁶⁵ ⁶⁶ ⁶⁷ ⁶⁸ ⁶⁹ ⁷⁰ ⁷¹ ⁷² ⁷³ ⁷⁴ ⁷⁵ ⁷⁶ ⁷⁷ ⁷⁸ ⁷⁹ ⁸⁰ ⁸¹ ⁸² ⁸³ ⁸⁴ ⁸⁵ ⁸⁶ ⁸⁷ ⁸⁸ ⁸⁹ ⁹⁰ ⁹¹ ⁹² ⁹³ ⁹⁴ ⁹⁵ ⁹⁶ ⁹⁷ ⁹⁸ ⁹⁹ ¹⁰⁰ ¹⁰¹ ¹⁰² ¹⁰³ ¹⁰⁴ ¹⁰⁵ ¹⁰⁶ ¹⁰⁷ ¹⁰⁸ ¹⁰⁹ ¹¹⁰ ¹¹¹ ¹¹² ¹¹³ ¹¹⁴ ¹¹⁵ ¹¹⁶ ¹¹⁷ ¹¹⁸ ¹¹⁹ ¹²⁰ ¹²¹ ¹²² ¹²³ ¹²⁴ ¹²⁵ ¹²⁶ ¹²⁷ ¹²⁸ ¹²⁹ ¹³⁰ ¹³¹ ¹³² ¹³³ ¹³⁴ ¹³⁵ ¹³⁶ ¹³⁷ ¹³⁸ ¹³⁹ ¹⁴⁰ ¹⁴¹ ¹⁴² ¹⁴³ ¹⁴⁴ ¹⁴⁵ ¹⁴⁶ ¹⁴⁷ ¹⁴⁸ ¹⁴⁹ ¹⁵⁰ ¹⁵¹ ¹⁵² ¹⁵³ ¹⁵⁴ ¹⁵⁵ ¹⁵⁶ ¹⁵⁷ ¹⁵⁸ ¹⁵⁹ ¹⁶⁰ ¹⁶¹ ¹⁶² ¹⁶³ ¹⁶⁴ ¹⁶⁵ ¹⁶⁶ ¹⁶⁷ ¹⁶⁸ ¹⁶⁹ ¹⁷⁰ ¹⁷¹ ¹⁷² ¹⁷³ ¹⁷⁴ ¹⁷⁵ ¹⁷⁶ ¹⁷⁷ ¹⁷⁸ ¹⁷⁹ ¹⁸⁰ ¹⁸¹ ¹⁸² ¹⁸³ ¹⁸⁴ ¹⁸⁵ ¹⁸⁶ ¹⁸⁷ ¹⁸⁸ ¹⁸⁹ ¹⁹⁰ ¹⁹¹ ¹⁹² ¹⁹³ ¹⁹⁴ ¹⁹⁵ ¹⁹⁶ ¹⁹⁷ ¹⁹⁸ ¹⁹⁹ ²⁰⁰ ²⁰¹ ²⁰² ²⁰³ ²⁰⁴ ²⁰⁵ ²⁰⁶ ²⁰⁷ ²⁰⁸ ²⁰⁹ ²¹⁰ ²¹¹ ²¹² ²¹³ ²¹⁴ ²¹⁵ ²¹⁶ ²¹⁷ ²¹⁸ ²¹⁹ ²²⁰ ²²¹ ²²² ²²³ ²²⁴ ²²⁵ ²²⁶ ²²⁷ ²²⁸ ²²⁹ ²³⁰ ²³¹ ²³² ²³³ ²³⁴ ²³⁵ ²³⁶ ²³⁷ ²³⁸ ²³⁹ ²⁴⁰ ²⁴¹ ²⁴² ²⁴³ ²⁴⁴ ²⁴⁵ ²⁴⁶ ²⁴⁷ ²⁴⁸ ²⁴⁹ ²⁵⁰ ²⁵¹ ²⁵² ²⁵³ ²⁵⁴ ²⁵⁵ ²⁵⁶ ²⁵⁷ ²⁵⁸ ²⁵⁹ ²⁶⁰ ²⁶¹ ²⁶² ²⁶³ ²⁶⁴ ²⁶⁵ ²⁶⁶ ²⁶⁷ ²⁶⁸ ²⁶⁹ ²⁷⁰ ²⁷¹ ²⁷² ²⁷³ ²⁷⁴ ²⁷⁵ ²⁷⁶ ²⁷⁷ ²⁷⁸ ²⁷⁹ ²⁸⁰ ²⁸¹ ²⁸² ²⁸³ ²⁸⁴ ²⁸⁵ ²⁸⁶ ²⁸⁷ ²⁸⁸ ²⁸⁹ ²⁹⁰ ²⁹¹ ²⁹² ²⁹³ ²⁹⁴ ²⁹⁵ ²⁹⁶ ²⁹⁷ ²⁹⁸ ²⁹⁹ ³⁰⁰ ³⁰¹ ³⁰² ³⁰³ ³⁰⁴ ³⁰⁵ ³⁰⁶ ³⁰⁷ ³⁰⁸ ³⁰⁹ ³¹⁰ ³¹¹ ³¹² ³¹³ ³¹⁴ ³¹⁵ ³¹⁶ ³¹⁷ ³¹⁸ ³¹⁹ ³²⁰ ³²¹ ³²² ³²³ ³²⁴ ³²⁵ ³²⁶ ³²⁷ ³²⁸ ³²⁹ ³³⁰ ³³¹ ³³² ³³³ ³³⁴ ³³⁵ ³³⁶ ³³⁷ ³³⁸ ³³⁹ ³⁴⁰ ³⁴¹ ³⁴² ³⁴³ ³⁴⁴ ³⁴⁵ ³⁴⁶ ³⁴⁷ ³⁴⁸ ³⁴⁹ ³⁵⁰ ³⁵¹ ³⁵² ³⁵³ ³⁵⁴ ³⁵⁵ ³⁵⁶ ³⁵⁷ ³⁵⁸ ³⁵⁹ ³⁶⁰ ³⁶¹ ³⁶² ³⁶³ ³⁶⁴ ³⁶⁵ ³⁶⁶ ³⁶⁷ ³⁶⁸ ³⁶⁹ ³⁷⁰ ³⁷¹ ³⁷² ³⁷³ ³⁷⁴ ³⁷⁵ ³⁷⁶ ³⁷⁷ ³⁷⁸ ³⁷⁹ ³⁸⁰ ³⁸¹ ³⁸² ³⁸³ ³⁸⁴ ³⁸⁵ ³⁸⁶ ³⁸⁷ ³⁸⁸ ³⁸⁹ ³⁹⁰ ³⁹¹ ³⁹² ³⁹³ ³⁹⁴ ³⁹⁵ ³⁹⁶ ³⁹⁷ ³⁹⁸ ³⁹⁹ ⁴⁰⁰ ⁴⁰¹ ⁴⁰² ⁴⁰³ ⁴⁰⁴ ⁴⁰⁵ ⁴⁰⁶ ⁴⁰⁷ ⁴⁰⁸ ⁴⁰⁹ ⁴¹⁰ ⁴¹¹ ⁴¹² ⁴¹³ ⁴¹⁴ ⁴¹⁵ ⁴¹⁶ ⁴¹⁷ ⁴¹⁸ ⁴¹⁹ ⁴²⁰ ⁴²¹ ⁴²² ⁴²³ ⁴²⁴ ⁴²⁵ ⁴²⁶ ⁴²⁷ ⁴²⁸ ⁴²⁹ ⁴³⁰ ⁴³¹ ⁴³² ⁴³³ ⁴³⁴ ⁴³⁵ ⁴³⁶ ⁴³⁷ ⁴³⁸ ⁴³⁹ ⁴⁴⁰ ⁴⁴¹ ⁴⁴² ⁴⁴³ ⁴⁴⁴ ⁴⁴⁵ ⁴⁴⁶ ⁴⁴⁷ ⁴⁴⁸ ⁴⁴⁹ ⁴⁵⁰ ⁴⁵¹ ⁴⁵² ⁴⁵³ ⁴⁵⁴ ⁴⁵⁵ ⁴⁵⁶ ⁴⁵⁷ ⁴⁵⁸ ⁴⁵⁹ ⁴⁶⁰ ⁴⁶¹ ⁴⁶² ⁴⁶³ ⁴⁶⁴ ⁴⁶⁵ ⁴⁶⁶

have been seen in some instances of lupus vulgaris (F. Koch⁸⁷³). The different appearance of tuberculosis of the bones is emphasized by Naegeli⁸⁷⁴.

Lymphadenopathy is a common feature. The peripheral as well as the visceral lymph nodes, especially those at the hilus, are frequently enlarged. Schramm⁸⁸⁴ found specific sarcoid tissue in the tonsils in all of his cases, and there is enough autopsic evidence that practically all organs may become the site of hematogenous metastases.⁷³⁰ Marked monocytosis, sometimes as high as 40 per cent, is a frequent though not invariable sign, which Pinner⁷³⁰ believes to be the hematological manifestation of a monocytic proliferation which also leads to the epithelioid granulomata.

It seems that sarcoid is relatively frequent in the American Negro.⁸⁷⁶



Fig. 117.—Brock's case. (Courtesy Dr. M. Jescher.)

The *microscopic* structure of the lesions is better characterized by the term noncaseating tuberculosis⁷³⁰ than by the rather vague word sarcoid. Dense foci of epithelioid cell tubercles are separated by areas of connective tissue. There is no caseation and little or no lymphocytic infiltration surrounding the lesions, so that the apt term naked tubercle has been used. Giant cells may be found.

⁸⁷³F. Koch, H. G. *Über tuberculöse multiple Syphiliden (Jahrg. 6.) bei Lupus vulgaris*. *Dtsch. Wochenschr.* 1935; 11: 919-9-1.

⁸⁷⁴Naegeli, S. *Über die histologische Unterscheidung der tuberculösen und der syphilitischen Hautkrankheiten*. *Monatsschr. Derm. Syph.* 1934; 30: 59-75.

⁸⁷⁶Norland, R. *Hematogenous Cutaneous Tuberculosis ("Sarcoid") in Negroes*. *Arch. Dermat. Syph.* 30: 59-75, 1934.

According to Pinner tubercle bacilli have been found in the lesions 25 times. This is a small percentage but considering the law of Jadassohn and Lewandowsky the scarcity of microorganisms must be expected in tuberculous structures and cannot be interpreted against the etiology in question. The fact that in a considerable number of instances tubercle bacilli have been demon-



FIG. 118. Boeck's sarcoid. (Courtesy Dr. M. J. Jones.)

strated in the lesions is a good argument for the tuberculous etiology of Boeck's sarcoid. Kark¹⁶ showed that during the first days of a crop of typical Boeck's sarcoid tubercle bacilli were numerous in the still erythematous lesion. There were perivascular foci of non-specific inflammation. Around the eleventh day the acid fast bacilli became scarce and epithelioid cell began to group together.

¹⁶Kark, J. H. & H. G. W. H. (see Boeck and J. Lupot). Beitrag zur Frage der tuberkulösen Ätiologie des Boeck'schen Sarcoides. Arch. f. Dermat. u. Syph. 121: 33-65, 1911.

On the thirty sixth day the typical sarcoid structure with epithelioid cell tubercles and giant cells was fully developed but no bacilli could be found. In the early stages the blood too contained tubercle bacilli⁸⁷⁷ (see also Leitner⁸⁸¹).

The tuberculin reaction is negative often even to 1 mg of tuberculin or only slightly positive in the great majority of the cases. This anergy is much too frequent to be explained by freedom of tuberculosis infection. Negative tuberculin reactions have even been found in cases of Boeck's sarcoid with frank tuberculosis^{733 734 877 878}. Zieler^{7 9} however observed that the tuberculin reaction which had been negative in a case of lupus pernio became positive with the



Fig. 119.—Boeck's sarcoid. (Courtesy Dr. M. J. A. S.)

outbreak of pulmonary tuberculosis. Lupus pernio is closely related to Boeck's sarcoid. Pinner³⁰ calls anergy an essential feature of the disease. Reactivity inhibiting substances in the serum so called anticutins could be demonstrated in four out of eleven patients with sarcoidosis which is less often than anergy⁷³ but probably more frequent than in normal or tuberculous patients. In several animals e.g. rats dogs cats foxes and horses tuberculosis takes much more often than in man a sarcoid like course with epithelioid cell tubercles absence

⁸⁷⁷Martenstein H. "a kofl Boeck und Lupus" inulo Arch f Dermat u Syph 1897 "O 10 4

⁸⁷⁸Jadassohn W. L'origine tuberculeuse de la maladie de Boeck Bull Soc fra c de dermat et syph 11 1344 1347 1934

of caseation, anergy and anticutins in the serum. This fact furnishes a parallel which can also be used in favor of a tuberculous character of Boeck's sarcoid.⁸⁷⁵ Finally combination with and transition into frank tuberculosis has frequently been observed. St. Epstein⁸⁴⁵ found progressive pulmonary tuberculosis in about 12 per cent and less active forms in a still higher percentage⁸⁷⁹ sometimes with disappearance of the sarcoid lesions. Appearance of the first lesion at the site of trauma⁸⁸⁰⁻⁸⁸¹ does not necessarily mean ectogenous infection since the trauma may lower the local resistance and attract the bacteria from the bloodstream. In this connection it may be mentioned that subcutaneous injections of many



Fig. 1. —Boeck's sarcoid. (Courtesy Dr. McIlam.)

substances especially oils may cause reactive changes of great similarity to sarcoid. The majority of the authors now seem to favor a tuberculous etiology of Boeck's sarcoid while dissenting writers among them Kissmeyer⁸⁸² who has wide experience with this rather rare disease hold that the disorder is a specific nosological and etiological entity. Kissmeyer⁸⁸² bases his opinion on the too rare and in his opinion not always valid findings of acid fast bacilli on the

⁸⁷⁵Ronches F. Sarcoidosis—Ca. With Autopsy Arch. Dermat. & Syph. 46 860-871 194

⁸⁷⁶Worster H. R. and Wiedner L. M. Sarcoid (Boeck Type) Arch. Dermat. & Syph. 22 343 1930

⁸⁷⁷Cougrout H. and Blum P. Tuberculose sarcoides hypodermiques par corps étrangers à la suite d'infection de vaccin tétanique néoplasiques Bull. Soc. franç. de dermat. et syph. 29 1651 1931

⁸⁷⁸Kissmeyer A. Contribution à l'étude clinique des sarcoides Bull. Soc. franç. de dermat. et syph. 41 110-1109 1934

⁸⁷⁹Blum P. A. Beitrag zu Ätiologie und Klinik des Boeckschen Sarkoids Hospitalstid. 1932 II 104-10 9 211 44 337

benign course on a refutation of J. Jadassohn's theory of positive energy and other reasons*. Some writers believe that the disease has the characteristics of a chronic bacillary granuloma with features relating it to tuberculosis, syphilis and also to leprosy⁸⁷⁹⁻⁹³⁴ while Rabello Jr.⁸⁸⁶ thinks that tuberculosis, leprosy and perhaps still another disease may produce Boeck's sarcoid. Arénic has a distinct therapeutic influence. This fact has been used as an argument against the tuberculous etiology.

Lupus Pernio—Lupus pernio is closely related to Boeck's sarcoid⁸⁶¹⁻⁸⁹⁷. It manifests itself as ill defined cyanotic cutaneous and subcutaneous nonulcerative plaques most frequently found on the nose and cheeks with marked symmetric tendency. On glass pressure lupus like spots can be demonstrated. This rare and chronic disorder affects mostly adults and is combined with bone alterations which resemble those found in Boeck's sarcoid. Histology and marked positive energy to tuberculin are further links to that disease and thus to tuberculosis.³³⁶⁻³⁴⁻⁸⁵⁵⁻⁸⁷⁷⁻⁸⁹⁶

Erythrodermia Exfoliativa (Pityriasis Rubra of Hebra)—Universal redness, infiltration and scaling accompanied by lymphadenopathy may be a phase in many diseases e.g. leukemia, arsenic poisoning, psoriasis, eczema and many others. Jadassohn⁸⁸⁷ in an analysis of 18 cases revealed that in at least eight pulmonary and other forms of active tuberculosis were present. Since then many such cases have been described.⁸⁸⁸

Purpura Hemorrhagica—The whole syndrome of hemorrhagic purpura even purpura fulminans (Gaede et al.⁸⁸⁹) may be produced by tuberculous infection. Miliary tuberculosis of the spleen seems to be especially predisposing particularly in children.⁸⁹⁰⁻⁸⁹¹ Cases with a fulminating course of less than one day have been observed. The number of cases of mild and severe purpura occurring in many types of visceral tuberculosis is considerable so that coincidence is unlikely. Some purpuric spots could be shown to possess tubercular structure.³⁸⁸ This corresponds to experiences with other purpuric infectious efflorescences e.g. the rickettsioses and bacterial meningitis. An old report of a finding of tubercle bacilli in purpuric skin lesions (Beirsemde and River 1906 after Volk⁸⁹²) does not seem to have been confirmed more recently.

Similarly Leitz⁸⁹³ in a recent review interprets the negative tuberculin reaction against a tuberculous etiology. He also questions the validity of some of the positive findings of tubercle bacilli.

⁸⁷⁹Klimmeyer A. La maladie de Boeck. "Les eczémas cutanés à l'origine multiples." *Tréface d. J. Darl.* Paris 193. Masson & Co.

⁸⁸⁰Rabello Jr. F. Doenças ouveles sobre a etiologia da afecção de Boeck e Boeck. *rol de la lepra.* Ann. d. Dermat. et Syph. 7: 571-597. 1936.

⁸⁸¹Kobayashi F. Lupus pernio mit Inosin. *Arch. J. Dermat. & Syph.* 31: 1-69. 1973. 31: 41-113.

⁸⁸²Jadassohn J. Pityriasis rubra Hebra und ihre Beziehungen zu Tuberkulose. *Arch. f. Dermat. u. Syph.* 23: 911-1891. 24: 273-463. 1922.

⁸⁸³Baran y III. Pityriasis Rubra (Hebra). *Arch. Dermat. & Syph.* 18: 716-729. 1934.

⁸⁸⁴Gaede M. S. and Vaughn J. O. Miliary Tuberculosis With Purpura in Infancy. *Am. J. Dis. Child.* 42: 869-873. 1931.

⁸⁸⁵Quilley A. J. The Hemorrhagic Diathesis and the Etiology of Hemophilia. Springfield, Ill. 194.

⁸⁸⁶Weiner J. J. and Cart. H. P. Acute Thrombocytopenic Purpura Hemorrhagica Associated With Tuberculosis (Miliary) of Spleen. Splenectomy With Recovery. *Ann. Surg.* 112: 57-61. 1941.

Scrofulosis (Scrofula) —Scrofulosis is a syndrome of nontuberculous inflammatory alterations in a child with tuberculosis predominantly of the lymphatic nodes of the neck and of the bones.⁸⁹ The characteristic combination of swollen or abscessed submaxillary or cervical lymph nodes eczema especially



Fig 121 —Pityriasis rubra (pityriasis rubra) (Courtesy Dr. M. Jenner)

around the mouth blepharitis phlyctenules conjunctivitis otitis media and rhinitis used to be a most common sight in the pediatric clinics of Europe. Scrofulosis is today rare in America⁹⁰ and has also decreased in other countries. Landis⁹¹ believes that scrofula is an infection with the bovine type of the tubercle bacillus. He explains the disappearance of scrofula with the pasteurization of milk. The tuberculin reactions in scrofulous children are strongly positive.

Avian Tuberculosis —Human infections with tuberculosis of birds usually chickens may lead to severe systemic and cutaneous diseases which have re-

⁸⁹M. J. A. B. La scrofula: une éruption et une conception nouvelle. *Paris Méd* III 13 00

⁹⁰La B. H. R. M. The Disappearance of Scrofula. *Am R. Tuberc* III 19: 01 1930

semblance to all known types of human tuberculosis but do not quite fit into the familiar pictures. Thus apthous and septicemic sarcoid gummatous and ulcerative forms have been described.^{366 394-396}

The diagnosis will rest on the chicken experiment, the positive von tuberculin test and the bacteriological culture. The cases seem to be rare. However the diagnosis is important since specific tuberculin treatment has been effective in the cure of such patients (Lowenstein and Joannovic quoted by Urbach³⁹⁷).

Lupus Erythematosus Chronicus

The term lupus erythematosus (erythemateux) was coined in 1851 by Cazenave in a clear differentiation from other forms of lupus as many destructive dermatoses were called. Cazenave (after the French text given by Paul Rich-



Fig. 12 —Lupus erythematosus discoid

ter³⁹⁷) describes this form of lupus as one which destroys superficially and which does not develop tubercles (which in Cazenave's time meant ulcerating nodules). The relationship of the disease which we now call lupus vulgaris to tuberculosis was then of course not yet understood because our present conception of tuberculosis which is based on the presence of the tubercle bacillus or its derivatives did not yet exist. In 1884 Robert Koch demonstrated by culture and animal experiment the tubercle bacillus in lupus vulgaris. After Koch the term lupus became definitely associated with tuberculosis. Despite the fact that Koch dealt

³⁶⁶Urbach F. Das Krankheitsbild der Gfugertuberkulose in Haut und im Tier. Arch. f. Dermat. u. Syph. 187 360-341 1929.

³⁶⁶Lowenstein F. Das Krankheitsbild der Hühnertuberkulose im Menschen. Schweiz. m. J. Wehnach. 2 804-810 1933.

³⁶⁶Koch R. Gfugertuberkulose. Verhandl. d. Internat. Kongr. Dermat. 2 69-72 1906.

³⁹⁷Richter J. Geschichte der Derm. 11. Ha. 1b f. H. u. Ok. 11 1906 10 4.

with lupus vulgaris only his work had the effect of stimulating research to prove the hypothesis of a tuberculous nature of lupus erythematosus also

The French dermatologists under Besnier's influence generally adopted the tuberculous etiology of lupus erythematosus while the majority of the German authors concerned with the question rejected this theory for a long time. Later on the Germans gradually and very reluctantly became more inclined to acknowledge the importance of tuberculosis in the etiology of lupus erythematosus



Fig 13—Lupus erythematosus chronicus

In the lesions of lupus erythematosus the *tubercle bacillus* has rarely been demonstrated with the Ziehl-Neelsen stain.^{29 308} In several instances acid fast bacilli closely resembling the tubercle bacillus have been found in the sediment from tissues destroyed with antiformin. The etiological significance of these findings must be considered doubtful because such para-tubercle bacilli have been found in many media and the antiformin method does not permit the differentiation of bacilli originating from the surface from those from the depth. In spite of negative control tests in normal skin³⁰⁹ these antiformin findings have not been acknowledged as an etiologic proof.^{789 829}

As far back as 1906 Gougerot succeeded in demonstrating the presence of the tubercle bacillus in the lesions of lupus erythematosus by means of animal inoculation. The findings have been confirmed several times^{729 900} though a great

²⁹Friedlaender D. The Etiology of Lupus Erythematosus. Special Reference to Tuberculosis. *J. Cutan. & Genito-Urin. Dis.* 29:417 1911.

³⁰⁸Vellet F. Lupus erythematosus. *Caz. n. e.* H. ed. d. H. u. Gk. 10:1 647 9 1931.

³⁰⁹Illich Br. and Fuhr H. Chronic Lupus Erythematosus and Tuberculosis. *Arch. f. Dermat. & Syph.* 116:742 1913.

semblance to all known types of human tuberculosis but do not quite fit into the familiar pictures. Thus aphthous and septicemic sarcoid gummatous and ulcerative forms have been described^{366 394, 398}

The diagnosis will rest on the chicken experiment the positive avian tuberculin test and the bacteriological culture. The cases seem to be rare. However the diagnosis is important since specific tuberculin treatment has been effective in the cure of such patients (Lowenstein and Joannovic quoted by Urbach³⁹⁹)

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³⁹⁶Urbach L. Das Erythema discoidale (discoide) der Haut beim Menschen und beim Tier. Arch. f. Dermat. u. Syph. 187: 360-361 1909

³⁹⁷Lowenstein E. Das diskoidale Hühner tuberkulose beim Menschen. Schweiz. m. f. Wochenschr. 2: 805-810 1934

³⁹⁸Kerl W. Gefäß tuberkulose. Verhandl. d. 1. internat. Kongr. Dermat. 2: 69-72 1936

³⁹⁹Nicht P. Geschichte der Dermatologie. Handb. f. H. u. C. K. 16: 2706-1934

observations carry as little weight in the discussion of the tuberculous etiology of lupus erythematosus as the successful treatment with tuberculin. One should also remember that nonspecific focal reactions have been seen after injections of many substances e.g. gold milk and other foreign proteins sulphur etc.

It is important in the discussion of the tuberculous origin of lupus erythematosus to consider whether or not this condition is *more frequently found in tuberculous than in nontuberculous individuals*. The opinions on this are extremely contradictory. Goeckerman⁹⁴ denies that lupus erythematosus is substantially more frequently associated with tuberculosis (36 per cent) than other dermatoses (32 per cent). The number of authors who believe that lupus erythematosus is a disease of persons with tuberculosis especially pulmonary and glandular is large. Ehrmann and Filkenstein⁹⁵ claim that tuberculosis could be demonstrated in about 50 per cent of the acute cases of lupus erythematosus in about 80 per cent of the chronic cases of lupus erythematosus with acute exacerbation and in 98 per cent of chronic lupus erythematosus. Oro's⁹⁶ figures run similarly high. Pautrier and Schaaff⁹⁷ give 72 per cent. The most recent survey is that of St. Epstein⁹⁸ who examined 200 cases of lupus erythematosus in 7.2 per cent of which active tuberculosis of the lungs could be demonstrated by X-ray. This is much less than in cutaneous tuberculosis (16.1 per cent) but much higher than in the controls (3.7 per cent) which were taken of the syphilitic patients in the hospital.

On the other hand in a great number of cases it has been impossible to produce any evidence of tuberculosis either during life or post mortem. Of course the value of such negative findings is always limited because small foci can easily be overlooked. The complement fixation tests with the antigens of Besredka, Calmette, Ponndorf and others did not corroborate the tuberculous origin of lupus erythematosus.⁹¹ *Combination with skin tuberculosis* such as lupus vulgaris, scrofuloderma or the so called tuberculids has quite often been reported. Lewandowsky⁹⁹ wrote in 1916 that the reports about the combination of lupus erythematosus and tuberculids had lately become too numerous to be explained by coincidence. Since then the reports have multiplied. Practically every type of skin tuberculosis has been seen in combination with lupus erythematosus. Lupus erythematosus as well as skin tuberculosis being rare diseases the number of reported combinations seem to exceed by far the rate of pure coincidence. Urbach¹⁰⁰ saw lesions of lupus erythematosus the diagnosis of which he secured by histological examination develop in the neigh-

⁹⁴ Goeckman W. H. I. Lupus Erythematosus discoides chronicus due to Tuberculosis? Arch. Dermat. & Syph. 3: 745-761, 1911.

⁹⁵ Ehrmann & Filkenstein. Lupus erythematosus. Arch. f. Dermat. u. Syph. 141: 408, 1927.

⁹⁶ Pautrier L. M. and Schaaff. Results of Sytematic X-ray Examination of Lungs in 29 Cases of Lupus Erythematosus. Zbl. 55: 0.

⁹⁷ Huberhain K. Kompliment in der Tuberkulose mit besonderer Berücksichtigung der Hauttuberkulose. Die komplimentäre tuberkulose im Lupus erythematosus. Acta Dermat. u. Syph. 7: 315-319, 1911.

⁹⁸ St. Epstein F. Lupus erythematosus in der Haut. Ungewöhnliche Fälle in der Skrofuloderma. Zbl. 11: 200, 1924.

borhood of a tuberculous fistula. Stuhmer²¹⁰ saw true lupus nodules in the scar of lupus erythematosus. The rarity of such observations in America may be explained by the fact that cases of skin tuberculosis are only about one tenth as frequent in North America as they are in Central Europe. As mentioned before, lupus erythematosus is about as common in America as it is in Europe. This lack of parallelism seems to indicate that lupus erythematosus in spite of many relations to tuberculosis is governed by another law than true tuberculosis of the skin.

Without going into detail it may be mentioned that evidence of similar character as that in favor of a tuberculous etiology has been produced in support of other bacteria, syphilis, mechanical trauma, cold, light and other agents.

Thus in spite of the great efforts which have been made the role of tuberculosis in the etiology of lupus erythematosus chronicus remains controversial.

Lupus Erythematosus Acutus

The most important systemic relationship of lupus erythematosus exists in the rare cases in which the dermatosis either starts with an acute dissemination or where an apparently chronic lupus erythematosus changes its character and becomes acute (*Lupus erythematosus acutus* and *lupus erythematosus chronicus cum exacerbatione acuta*).

Transitional cases between all types of lupus erythematosus have been demonstrated. They prove the close relationship of the various types.

The acute form of lupus erythematosus seems to occur in *all ages* but the majority of the patients are those in the third and fourth decade.

The sex distribution of the acute forms has the ratio of three females to one male. This ratio is based on a review of 100 cases published in the last twenty years.

Many factors can change the character of chronic lupus erythematosus into the acute form. Known to have provoked acute lupus erythematosus are exposure to sun and to strong artificial light^{9, 10, 11}, bee stings applied for the treatment of arthritis¹², mosquito bites, gold therapy, trivial infections like otitis media¹³ or such following tooth extraction¹⁴, lymphangitis¹⁵, polyarthritis¹⁶ and physical and mental strain¹⁷. In many cases, however, the disease apparently begins without any such factors.

Various authors. Lupus erythematosus. Symptom on Argument for and Against Tuberculous Nature. Dermat. W. bischr. 99: 1346-136, 1934.

¹ Roxburgh A. C. Acute Disseminated Lupus Erythematosus. Five Fatal Cases. Brit. J. Dermat. 45: 110, 1933.

² Hoffman. Lupus erythematosus. Zbl. 27: 75-10, 1902.

³ Jiles J. H. Generalized Lupus Erythematosus and Intra-abdominal Tumor. Am. J. Dis. Child. 28: 13-131, 1914.

⁴ Gruhl O. Beitrag zur Klinik und Histologie des Lupus erythematosus acutus. Arch. f. Dermat. u. Syph. 187: 575-576, 1914.

⁵ Valli S. Pathogenes und pathologische Anatomie des Lupus erythematosus acutus. Monatsschr. Z. 9: 19-19, 1911, 35: 13, 1911.

⁶ Clark E. H. and Walker A. W. Lupus Erythematosus Acutus. Dis. of the Skin. Calif. Med. & West. Med. 24: 354-357, 1916.

⁷ Gibson R. Fatal Case of Lupus Erythematosus. With Post Mortem. Brit. J. Dermat. 27: 107, 1915.

⁸ Fagman M. E. Jr. Early Acute Lupus Erythematosus. Arch. Dermat. & Syph. 35: 645-607, 1937.



Fig 1 4 —Lupus erythematosus acutus (Courtesy Dr. M. J. Jenner)



Fig 1 5 — Subacute lupus erythematosus in phrygian. Exacerbation after prolonged exposure to sunlight early in spring

The *onset* may be sudden with chills, high temperature and all the symptoms of an acute infection. However, there are cases starting with relatively mild attacks of skin eruptions even without fever. Excessive fatigue is an outstanding complaint.

The most constant early cutaneous lesion is the appearance of sharply outlined red patches on the face. These *erythemas* are often arranged in butterfly or bat shape, covering the nose and the malar prominences, the ears, especially the upper parts of the helix, the chin and the neck. Here the erythema is often limited to the lower anterior part of the neck. V, which particularly in women is exposed to the light. The erythema is often but not always edematous or vesicular, especially in severe cases. The rash can simulate erysipelas but the symmetry, the development from a number of small individual erythematous lesions, the comparative stability and the course will soon differentiate the two. In the edema the follicles appear more open, creating an orange peel like surface.



Fig. 1. Lupus erythematosus, acute dissemination after first prolonged exposure to sunlight. Scalp lesion with loss of hair and well open follicles.

The simultaneous appearance of lesions of the scalp and fingers is very characteristic. The so-called erythema perstans of the face may remain throughout the whole course of the disease. It may disappear and recur. The erythematous eruptions may spread over large areas, even over the whole body surface. Exudative features like vesicles, blisters and crusts sometimes create an eczematous, impetiginous or even pemphigoid appearance. Hemorrhagic lesions, mostly of small size, have often been observed.

In some cases the skin lesions have a more exanthem-like appearance, described as a roseola or as a morbilliform rash. Often the skin lesions appear in crops which fade or heal and recur often after intervals of indefinite length. It is a definite characteristic of the dermatosis to center about the nose and neck. Here the lesions are redder, more deeply infiltrated, more constantly observed and healing with atrophy is more frequent than in other sites.¹¹ More or less acute oral and tonsillar infections are not uncommon.

In acute lupus erythematosus the cutaneous eruption is *not* the most important part of the picture. It is the syndrome of a severe systemic infection or toxic reaction which determines the picture and the course. Continuous high fever is an almost regular symptom. General malaise and later on prostration and exhaustion are frequent.

Fig 127

Fig 128



Fig 129

Fig 127 - Lupus erythematosus acutus (Patient of Dr. S. Rosenthal)

Fig 128 - Lupus erythematosus acutus. Detail of face. Note open follicles (Patient of Dr. S. Rosenthal)

Fig 129 - Lupus erythematosus acutus. Effluvia apillorum during prolonged illness (Patient of Dr. S. Rosenthal)

Lymphadenitis arthritis and more often arthralgia without true arthritis are other septic symptoms. The joint pains frequently accompany the acute exacerbations. The spleen is often enlarged.

Nephritis often with a high albumin content of the urine is one of the most constant and often early complications. *Retinitis albuminurica* has been seen several times. *Hematoporphyrin* in the urine is a frequent finding in acute lupus erythematosus especially in the severe cases. The photosensitizing effect of hematoporphyrin is well established.⁸⁸ *Colitis* and *enteritis* often not only cause diarrhea but severe abdominal pain which has caused unnecessary appendectomies in several instances.⁸⁹ *Endocarditis*, *myocarditis* and *bronchopneumonia* are common and together with renal failure frequently the immediate cause of death.



Fig. 130. Lupus erythematosus acutus. Not center of rash in neck & area. (Courtesy Dr. M. J. Jones.)

The blood cultures done in a great number of cases of acute lupus erythematosus have usually been negative. Occasionally streptococci were found⁹⁰⁻⁹² and very rarely staphylococci and bacterium coli. These and some other findings probably are terminal or incidental. The largely negative blood cultures indicate toxemia rather than bacteremia.

Leukocytosis of 15,000 or more has been observed several times but it is the exception. Much more frequently the white count is low, even as extremely low as 800. It has been emphasized⁹² that even complications like pneumonia, pleurisy, nephritis and endocarditis failed to raise the low white count. The

⁸⁸B. Ling, F. A. J. Barwitz, J. Akténisch, *Erkrankungen der Haut*, 4:1:4:169, 1932.

⁸⁹Rose, F. A. J. Colberg, L. C. *Lupus Erythematosus*. Visceral Lesions of Acute Disseminated Lupus Erythematosus. North America, 19:333, 1935.

⁹⁰O'Brien, K. I. *Lupus erythematosus acutus*, Zbl. 21:139, 1917.

⁹¹Simon, H. W. *Zur Klinik und Ätiologie des Lupus erythematosus acutus*. Münch. med. Wchnschr. 72:1073, 1076, 1927.

⁹²Wendt, H. *Lupus Erythematosus*. J. Clin. Disease. Münch. med. Wchnschr. 81:217, 1934.

granulocytes are the elements which suffer most while the lymphocytes prove to be more resistant so that a relative lymphocytosis may result. Aneosinophilia is another frequent and unfavorable occurrence. The reappearance of the eosinophiles often accompanies improvement and remissions. Purpuric spots, petechial showers and thrombocytopenia are recognized features of the syndrome.^{92-93a} Wendt emphasizes that his patients with leukopenia, thrombopenia and purpura had not received gold treatment which can cause similar lesions.

Secondary anemia is frequent. The sedimentation rate is often increased.



Fig. 131 - Petechia in lupus erythematosus acutus

Acute lupus erythematosus is a very dangerous disease in both its form though the acute exacerbation of a pre-existing chronic discoid lupus erythematosus has a better chance to heal or to return to the chronic stage than have the primarily acute cases.⁹⁹ Out of 100 cases published from 1920 to 1940 at least 76 ended fatally. Recovery being rare only a few cases of the transition of true acute lupus erythematosus into the chronic discoid form have been observed.⁹³ⁱ

The gross pathologic findings consist of a variety of septic, renal, pulmonary and liver changes, splenic infarcts and muscular and valvular heart lesions.^{93j}

In 111 autopsies in acute lupus erythematosus (Grawalowski^{93k}) tuberculosis was the sole finding in somewhat more than 50 per cent. In less than 50 per cent there were no traces of tuberculosis but usually another bacterial infection was present. Other experiences were similar.

⁹² Rose F. and Phillips D. M. Acute Disseminated Lupus Erythematosus. Systemic Disease. Ann. Int. Med. 12: 951-963, 1933.

^{93a} K. H. H. Lupus Erythematosus and Its Morphologic Variants With Particular Relation to Systemic Lupus Erythematosus. Arch. Dermat. & Syph. 36: 7-9, 757, 1937.

^{93b} Gulon C. M. and Adam F. C. Six Autopsied Cases of Disseminated Lupus Erythematosus. Am. J. M. Sc. 205: 33, 1943.

^{93k} Grawalowski K. Lupus erythematosus acutus. Pled. ritiqu. Acta dermat. venerol. 11: 1-39, 1939.

It is likely that the twenty cases of erythema with visceral lesions described by William Osler³²⁷ in 1904 included cases of lupus erythematosus acutus. The outstanding lesions were purpura erythema colic nephritis and arthritis. There is little clinical or post mortem evidence of endocarditis.

The Libman Sacks syndrome^{328, 329} consists of a peculiar verrucous endocarditis differing from that in rheumatic fever mainly by the absence of Aschoff bodies. The patients are mostly young females. Six out of eleven had lupus erythematosus, three more only erythema. Purpuric symptoms were common. Leukopenia and thrombocytopenia occurred. Pericarditis, arthritis and nephritis were found in almost every case.

It has been pointed out that all the symptoms of lupus erythematosus acutus are rather fluctuating. It is likely though not yet certain that the Osler³²⁷ erythema group and the Libman Sacks³²⁸ syndrome and acute lupus erythema to us form an entity which often but not always develops typical dermatomes. The fundamental and common pathology of the group can possibly be seen in the widespread vascular lesions of the finer ramifications described by Baehr, Klemperer and Schiffrin³⁴⁰. The lesions consisting in capillary dilation, endothelial proliferation, a peculiar hyaline degeneration, thrombosis and extravasation were found in all viscera in about 25 per cent of the cases but they were most frequent in the skin and in the kidneys. Glomerular changes of this kind make the thickened capillary wall appear rigid as if made of heavy wire. These wire loop lesions which were present in more than 50 per cent of the cases and which have been often confirmed^{341, 342} are very striking. The authors emphasize that they have not seen them in any other human disease except perhaps in eclampsia. Similar lesions were found in horses which had been immunized by frequently repeated intravenous injections of live bacteria especially of the pneumococcus streptococcus group.

More recently³⁴³ a new conception based on observations of physicochemical alterations in the fibers and ground substance of the connective tissue has been developed.

³²⁷Osler W. The Erythema Group of Skin Diseases. *Am J Hyg* 227: 1, 1904.

³²⁸Libman E. and Sacks B. A Hitherto Undescribed Form of Valvular and mural Endocarditis. *Arch Int Med* 32: 701, 1924.

³²⁹Boite C. H. and Rother H. V. Lupus Erythematosus—so-called Libman Sacks Syndrome—Relation to Dermatology. *Arch Dermat & Syph* 32: 642, 1936.

³⁴⁰Baehr E., Klemperer T. and Schiffrin A. *Tr A Am Hygien* 50: 130, 1930.

³⁴¹J. Reber. Lupus Erythematosus Associated With Visceral Vascular Lesions. *Q J of Autopsied Cases*, Bull. Joh. Hopkins Hosp 59: 62, 73, 1936.

³⁴²Denzel & Blumenthal. Acute Lupus Erythematosus Diseminatus. *Am J Dis Child* 52: 555, 1937.

³⁴³Klemperer P., Pollack A. B. and Baehr C. Acute Lupus Erythematosus. *New York State J Med* 42: 225, 1942.

Leprosarium in Carville Louisiana⁹⁵³ Great numbers of lepers live in the Philippines and in Hawaii where under American administration important scientific observations have been made The leper island of Culion in the Philippines and the Kala hospital of the United States Public Health Service in Honolulu have in many ways become model institutions Some authors think that leprosy existed in America before the voyage of Columbus

Etiology, Contagion—Leprosy is caused by the Hansen Neisser bacillus an acid fast rod which in many ways is related to the tubercle bacillus It stains best with the Ziehl Neelsen method but it is a little stouter and straighter more angular if bent and usually more numerous and more apt to form bundles than the tubercle bacillus

Culture as well as progressive infection of animals has not yet been accomplished in an entirely satisfactory and corroborated way Though this has hampered elucidation of many phenomena the etiologic role of the Hansen Neisser bacillus has been sufficiently demonstrated by its constant presence in almost all leprosy lesions in the blood in the majority of the organs in about 50 per cent of the cases and in all secretions as well as by its absence in other diseases and in healthy individuals from leprosy free surroundings

Leprosy is a moderately contagious disease The epidemiology is still contradictory Most individuals according to Muir⁹⁵⁴ nine out of ten seem to possess a high degree of *resistance* This is demonstrated by many instances of persons who remained healthy in spite of exposure to massive infection over a long period of time These were mostly family members who lived together with contagious lepers Conjugal leprosy is not common and contagion by intercourse occurs rarely Nurses and physicians caring for lepers have not very often become lepers It is hard to decide how much credit must be given to sanitary measures and avoiding contact

True congenital leprosy is rare Rodriguez⁹⁵⁵ did not find a single case in 871 children born of lepers in the Culion colony Many children in leprosy surroundings become infected early in life but many stay healthy⁹⁵⁶ Breast feeding is not an important factor in the transmission of leprosy from mother to child⁹⁵⁷ Contact with contagious lepers in close living quarters seems the main way of transmission but even under such conditions contagion does not invariably occur The author saw a leper covered with tuberculous lesions who lived for 16 years in one room with his family all members of which remained healthy

Though experienced leprologists believe that the leprosy bacillus does not live long outside the human body many authors are convinced that the disease can be carried by insects especially bedbugs and ticks and a variety of fomites

⁹⁵³Hopkins R and Fagot C H Report Ten 1 of Leprosy in the U S A JAMA 128 943 1944

⁹⁵⁴Muir F Importation of Natural Resistance in Leprosy Trans Far East A Trop Med 2 547 193

⁹⁵⁵Muir E Leprosy—Resistance and Typing of Skin Lesions Leprosy Rev 10 1 5 1939

⁹⁵⁶Rodriguez J Leprosy Statistics Philippines J N 27 453 19 6 31 31 29 J Philippines Islands M A 6 40 1935 6 4 12 6 8 33 19 4 9 417 10 9 Monthly Bull Philippines Health Serv 8 27 19 4 8 702 19 9 6th Congr Far East A Trop Med Tokyo 19 2 639 19 6

among which bedding plays a major role. Airborne droplets from coughing and sneezing may carry the microbes⁹¹⁸ but the importance of this way of transmission is controversial. The infection of the nose with the fingernails is important. Leprosy is mostly a disease of the underprivileged classes intimately connected with dirt, poor housing, poor diet and other unsanitary conditions.

Incubation, General Course, Types—The incubation period is extremely variable, the observations ranging from one week to as long as 32 years. The average may be one or a few years. Rodriguez⁹⁵⁶ in observations of children of lepers in Culon, found it to be three years nine months. The course of the manifest disease itself is extremely variable with regard to severity of symptoms, type of prevailing lesions, acute attacks, remission, complications and final outcome. In spite of all variations and transitions, three definite clinical types stand out:

Lepra lepromatosa (tuberous cutaneous leprosy, L type)

Lepra nervosa (anesthetic neural leprosy, N type)

Lepra mixta (L plus N type)

Lepra maculosa is not a type but rather a stage which may be encountered in any of the three types. One or the other type is usually predominant in an area, e.g. neural leprosy in China. The general rule that the neural type is more common in the tropics and the lepromatous variety in the temperate climates has many exceptions.

The Clinical, Especially Cutaneous, Symptoms of Leprosy

The Early Stages—The primary skin lesion is a round, pink, tan, copper-colored or whitish smooth, usually single macule of about 1 cm. which grows slowly up to several centimeters in size and may remain stationary over a long time. The surface is glossy and the edge slightly raised. Later when the periphery grows, the center appears depressed or even atrophic. Frequently there is a depigmented areola. Depigmentation more pronounced in the colored skin is often the most noticeable element⁹¹⁴. Sooner or later nervous signs and symptoms in the affected area start. A period of hyperesthesia or numbness⁹¹⁵ may precede the anesthesia. While the sense of temperature is most often the first to be disturbed, after a short time touch and pain and later the sweat secretion become equally impaired. The primary lesion is rarely an object of medical attention. It is hardly ever seen in the leprosarium in Carville, La. (Personal communication to the author). The best observations of initial manifestations were obtained by Rodriguez⁹⁵⁶ among the children of lepers in Culon in the Philippines. The primary lesions may look very trivial especially in the colored skin which becomes easily depigmented after scratches and banal pyogenic infections. However, the detection of anesthesia establishes the diagnosis of leprosy. Blisters are not very numerous in the primary lesions. Rodriguez⁹⁵⁶ found that the commonest initial sites were the buttocks, the cheeks, the posterior and lateral surfaces of the thighs and the loins. The experiences of other observers are similar⁹¹⁷. The primary lesion was never seen on the chest or the abdomen, a frequent site of later lesion.

The primary sore is often found on the *nasal mucosa*. Here it may appear as an ulcer of the anterior septum causing epistaxis which is a well known early symptom. Bacilli may usually be found early in the nasal mucus. Mouth and tonsils are other portals of entry.

Some authors believe that leprosy may develop without a primary lesion. In other cases nervous manifestations may be the first signals of the infection.

Since the primary lesion is frequently inconspicuous and without subjective symptoms the *diagnosis of leprosy is usually made after its generalization* which occurs through the bloodstream and the lymphatics.



Fig. 13 — Leprosy. Early pigmented and depigmented maculae. (Courtesy U. S. Marine Hospital, Caville, Ia.)

The following types of lesions, any of which may be noticed first, represent the most characteristic elements of *early generalized leprosy*.

1. *Erythematous maculae* of bluish or pinkish hue which in their early stages fade on pressure. The red spots start as small round lesions of less than 1 cm. in diameter but they grow, multiply, coalesce and form gyrate patterns. The later appearing lesions grow quickly. The individual lesion may disappear without any sequelae or may leave the skin pigmented or depigmented. Depigmented areolae and shift of pigmentation make them resemble primary lesions especially when greater activity causes infiltration. The red spots are found on the face, on the ears, buttocks, the extensor surfaces of the extremities and sometimes on the back. A fine dusty desquamation may be seen on the early macule.¹⁵⁷

2. *Pigmented maculae* which may be primary or develop from erythematous macules. At first they look like freckles or chloasma. Later they may grow to

¹⁵⁷Chiyuto S. and Yasuo F. Leprosy Monthly Bulletin, Philippine Health Service 11: 587, 1931.

hand size. Their distribution is that of the red spots. Sometimes they form gyrate or variegated patterns. There is neither infiltration nor desquamation. In their usually extremely chronic course they lead to nervous leprosy.

3 *Depigmented maculae* (White spots) which have no or only slightly infiltrated edges. They are not completely devoid of pigment but relatively light especially in the colored skin. The earliest white spots are perifollicular with slight follicular keratoses. They are 1 to 10 cm in diameter sometimes numerous and arranged in large network like patterns thus resembling tinea versicolor or vitiligo. Vitiligo however has more distinct borders and the depigmentation is more pronounced. Sooner or later anesthesia, loss of hair, anidrosis and other symptoms of nervous leprosy become manifest. The lesions may acquire an infiltrated active margin. Sometimes they become the site of vesicles or bullae. They may heal with scars.

4 *Local swellings, infiltrations and nodules* in early leprosy are often first noticed on the alae nasi, the ear lobes, the elbows and the knees. They usually develop in or close to the red spots and may become large plaques. They may be few in number or abundant. The cutaneous nodules vary from pinhead to walnut size. At first the surface is greasy and smooth, later dry and scaly, resembling psoriasis. They often appear in crops accompanied by fever and other general symptoms. They grow fast but their growth may become arrested in any stage and there may be no change for years. New nodules may appear around the old ones which may heal with a scar. Some nodules or deep painful ulcers especially under unsanitary conditions occur on the exposed areas of the skin. The ulcers may destroy tendons and muscle and the scars may lead to serious contractures and deformities and to strictures of the upper air passages.

Anesthesia at first only for heat and pain, later for touch, is common in the nodules. The bacilli are numerous.

5 *Blisters and bullae* of all sizes may appear on white or red macules or on the normal skin and may form torpid ulcers. The blisters are rare as early symptoms. Early microvesicular eruptions which microscopically proved to be lepra were seen in the Philippines in 16 of 40 children.²²

6 *Nervous disorders* especially disturbances of sensitivity may occur early and are not restricted to the visible lesions. Numbness, a leather glove feeling, itching and other *paresthesias* especially along the extremities may become very annoying.²³ *Hyperesthesia* may make the patients move slowly to avoid any touch. They may be unable to turn a key because the pressure of the key against the fingers causes severe pain. This phenomenon has been called the sign of the key by a leprosy doctor who discovered it in himself.

Pain on percussion of the bones especially the clavicles, the olecranon and the skull is often early and pronounced. The deep structures of the foot may be very painful on extension of the ankle joint.

Anesthesia a most important sign may develop in connection with visible lesions or independently in apparently normal skin. Rodriguez²⁴ found leprosy anesthesia fickle and variable and he failed to find anesthesia in cutaneous lesions in 16 per cent of the cases. The legs, dorsa of the feet, forearms, hands and

fingers in the order named are the most frequent sites of anesthesia⁹⁵⁶ Frazier⁹⁵⁵ emphasizes the peculiar dissociation of the elements of sensation. The perception of temperature disappears first. Then follows anesthesia for pain and finally for touch.⁹⁵⁶ Anesthesia of the little finger especially of the left little finger has often been mentioned as an early symptom. Early anesthetic areas are often found on the ulnar aspects of the forearms and hands and on the lateral surfaces of the lower legs and feet. The nervous disorder may appear on all kinds of macules and trophic ulcers may develop in all anesthetic areas. The superficial nerves most often the ulnar nerve the peroneal and the auricularis magnus may early become thickened and palpable. Atrophy of the musculi interossei and of the hypothenar eminences are further early nervous symptoms.

7 *Anidrosis* especially of the finger tips is an early symptom and may precede anesthesia. Some disturbance of the sweat secretion can be demonstrated in 70 per cent of the cases (Degotte after Fellner^{955 956}).

8 *Discoloration of the skin*: The skin often becomes gray or brownish. This is especially conspicuous in the white race. The colored skin has a tendency to become lighter. The skin sometimes takes on a senile and wrinkled appearance.

9 *General symptoms*: Chills fever anorexia nausea weakness muscular pains and other general symptoms of bacteremia and toxemia are very common. The fever may be accompanied by profuse sweating during which the patient may notice that parts of his body remain dry.

Lepromatous Leprosy.—In the lepromatous form the maculae show an early tendency to become infiltrated or nodular. Nodules may appear in varying numbers and sizes often on apparently normal skin without any inflammatory halo. The first stage may look like an acne papule then the lesion becomes firm shotty raised and glossy often with small telangiectasias. The color is pink in the early stages later purple brown copper or bronze. If regression occurs the epidermis of the lesions may peel. The lepromas are often warmer to the touch than the surrounding area. *Hyperesthesia and anesthesia are observed in almost all cases but the time of appearance and the site vary. If cut the patient may feel the touch of the knife but no pain. The lesions may coalesce and form plaques. Such large or small infiltrations may remain stationary for a long time and then resume their growth or undergo regression or ulceration which may partly by secondary infection reach a great depth and width especially in tropical countries. The ulcers may finally heal with scars which reflect the degree of destruction. All stages—infiltration single and coalescent nodules ulceration and scarring—may be encountered in the same patient at the same time so that an exceedingly multifiform picture results. The face is the main site of the nodular changes. The forehead the eyebrow region the nose the chin the lobes of the ears and finally the entire face may become involved. The development of the lepromas on the face is determined by the fibrous and muscular strictures. The fibrous strands crowd the infiltrates together into bulging tumors*

⁹⁵⁵Frazier C. N. Leprosy. Epitheliology and Natural History. J. A. M. A. 323: 476, 1947.

⁹⁵⁶Fellner M. Leprosy—Review of Literature for 1940. Dermatologia 48: 1-179, 1941.

⁹⁵⁷Fellner M. Leprosy. Dermatologia 50: 1-71, 1949.

and divide them by deep creases. Thus the lion face, the *facies leonina* of advanced tuberculous leprosy, results. Patients in this stage have an amazing similarity. It may be difficult to tell from the face whether the patient is young or old, man or woman, or even whether he is colored or white, since the colored skin often becomes lighter and the white skin darker. The nose becomes swollen, partly by specific involvement of the nasal mucosa which may lead to complete destruction of the septum with subsequent collapse of the nose. It is surprising that the sense of smell resists destruction for a long time. Corresponding lesions appear in the mouth, the pharynx and the larynx. There are infiltrations, ulcerations and scars with resultant deformations and strictures. The eyes become involved in nine out of ten fully developed cases. The scalp and Scarpa's triangle often remain free, and the trunk generally is not as heavily involved as the face. The buttocks are common sites of large nodular plaques.



Fig. 133.—1, pro-matou 1, prosy. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

Involvement of the *lymphatics* causes elephantastic changes, especially of the lower legs, with all the complications of the syndrome, such as recurrent erysipelas and fever, ulcerations and finally mutilations. The external genitalia are commonly affected. Every internal organ may take part in the process, though with great variations. In some cases the gastrointestinal symptoms dominate the picture; in others, respiratory or urinary complications dominate. The course usually stretches over many years, even 2 or 3 decades, although acute cases with exanthematic eruptions of lepromas on almost the entire skin

severe prostration of typhoid type and rapid fatal outcome are known. The chronic course is more or less often interrupted by acute febrile episodes, the lepra reactions or *acute attacks* which contrast strangely to the otherwise extremely chronic course. If the reactions are long and relapsing they may precipitate the outbreak of lepromas and aggravate the course. On the other



Fig 134 - Leprosy. Lepromatous eruption. (Court 219 Marine Hospital, Caville, La.)

hand, however, short reactions may exert a healing influence. Urticaria perstans like lesions of comparatively transitory character have often been seen to appear during the lepra reaction. Existing lesions may become edematous, erysipeloid or vesicular, indicating a severe focal reaction. Remitting fever, arthritic pains and general swelling and tenderness of the lymph nodes may accompany the reaction. The sedimentation rate is increased. The lepromin reaction (see below) is negative.



Fig 13 —Lep o y papular exanthema (Courtesy U S Marine Hospital Carville La.)



Fig 136 Leprosy Leproma. (Courtesy Dr E R Kirkpatrick)

J. Jadassohn^{22a} was the first to interpret the lepra reaction as a phenomenon of allergy to the leprosy bacillus. This opinion is today widely accepted.²⁴¹ Between the attacks periods of relative well being and regression of the lepromas may set in making the patients hopeful and believing that they are on the road to recovery. This hope is however too often deceptive. Suddenly fever herald



Fig. 137.—Advanced lepromatous leprosy. (Courtesy U. S. Marine Hospital, Carroll, La.)

a new outbreak with the appearance of new or the enlargement of old nodules. If the patient live long enough the healing tendency becomes more pronounced and gradual transition into atrophy and scarring may reach an *arrested state* which amounts to healing. Actual spontaneous and relatively sudden healing with regression of all lepromas occurs occasionally. In such favorable cases the bacilli disappear from the nose and after long observation such a patient may be considered healed according to our present knowledge. The neural form is more likely to become arrested than the lepromatous variety, but arrest or healing is the exception in both types. Ordinarily the patient is condemned to a long period of increasing suffering. The involvement of the ur passages and the eyes, the loss of voice, the general induration and infiltration of the skin, the nervous disturbances, the pain, the effort connected with the slightest movement, the terrific odor, diarrhea, and many other afflictions among which the mental suffering of being an outcast is not the least, must make death appear as a salvation. Pulmonary tuberculosis is a frequent complication and cause of death in advanced lepromatous leprosy.

^{22a}Pardo-Castell, V. and Tillet, R. Leprosy. Contribution of its Clinical Pathologic Immunologic and Bacteriologic Aspects. J. A. M. A. 121: 1261-1909, 1913.

Neural Leprosy —*Lepra nervosa* generally takes on a still more chronic course than the tuberculous form. Cases of 60 years duration are on record and long periods of apparent arrest may occur.

Fever and other general prodromes herald the cutaneous eruptions more frequently than in tuberculous leprosy.



FIG. 129. Neural leprosy. (From 1915 Division of Dermatology Department of Medicine University of Chicago.)

In the early stages the appearance of all three types of maculae—the red spots, the pigmented spots and the white spots—dominates the picture with a conspicuous absence of infiltrations and nodules. The distribution is usually fairly symmetric but varying in size and shape. Symmetric erythema nodosum-like eruptions occur. The spots become anesthetic within a few days. Blisters are common and may predominate so that a pemphigus-like picture results. However, Nikolsky's sign is negative. The bullae may increase peripherally surrounded by an inflammatory vesicular areola. Large bullae may form destructive foul ulcers which heal slowly. The ulcers are painless. In some cases no actual bullae develop but the epidermis forms a dry, scaly crust of yellowish-brown color. The predominantly bullous and ulcerative type of

leprosy is called *lazarine leprosy*. The content of the blisters contains many bacilli but the tissues are able to destroy them quickly so that they cannot be found in sections. The lepromin reaction is positive indicating good defense. The prognosis is relatively good.⁹⁶¹

Paresthesias, hyperesthesia and anesthesia are the common complaints of beginning neuritis. Muscular atrophy, paralysis and trophic ulcers follow later. Some of the nervous complications which predominate in *lepra nervosa* have already been described.



Fig. 139 — *Lazarine leprosy*. (Courtesy U. S. Marine Hospital, Cavalla, La.)

The affected nerves often become thick, spindle or rosary like so that they can be palpated. Sometimes only a relatively small area of the skin becomes anesthetic and the whole process may become arrested at this stage and stay so for a long time with no other symptoms until new similar crops continue the development.

Anesthesia, the most characteristic phenomenon of nervous leprosy, leads to ulcers and to mutilation. The feet, lower legs, hands and forearms are most commonly affected. Beginning at the little finger the anesthesia may involve the whole arm in similar fashion a leg may become anesthetic. Later on symmetry is pronounced. It must be stressed that anesthetic areas are not sharply bordered and that they do not exactly correspond to the nerve supply.

The successive impairment of the senses of heat, cold, pain, touch and pressure has been mentioned earlier. Deep muscular and joint perception remains intact. The mucosal surfaces may become anesthetic too. The scalp is seldom involved.

Muscular atrophy usually starts in the small muscles of the hands leading to a clawlike contracted hand which can hardly be moved. Similar equinovari deformities develop in the feet. After an initial increase in the reflexes disappear. Neuralgic pains in the trigeminal area are common. While total paralysis of the facial nerve is rare, the muscles which close the eyes are frequently paralyzed. Lagophthalmus, ectropium, loss of eyelashes and dryness of the conjunctiva finally lead

to the characteristic *rotunditas oculorum* which since the middle ages has been known to be characteristic of the leper. The empty stare of such eyes together with partial or total immobility of the face creates the typical *facies antonina*.

The skin as already mentioned generally becomes wrinkled, ashen or pigmented. Gradually the sebaceous glands disappear. The nails may partially or totally atrophy and disappear.

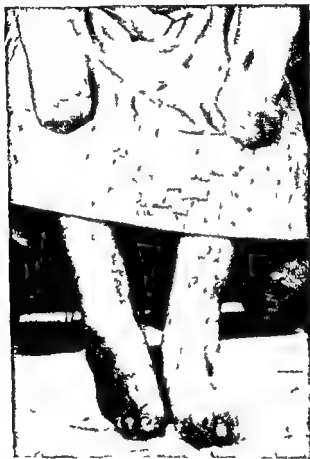


Fig 140 Leprosy Mutilation (Courtesy U. S. Marine Hospital, Cavell, La.)

Mutilations follow anesthesia. The destructive process may start with an abscess or trophic ulcer. Resorption of bones, especially of the fingers, may be a factor. The middle phalanx may disappear first so that by contraction the first and third phalanges become drawn together. Antrum-like stringulations are another feature. All the processes—anesthesia, muscular atrophy, trophic ulcers, bone resorptions, secondary infection and gangrene—may finally lead to the complete loss of fingers, toes, hands, feet and even whole extremities.

It is not surprising that mutilation and all the other sequels of the nervous involvement finally lead to cachexia. It is however most amazing that life

frequently continues for long years in spite of such destruction and suffering in which the body is dead before the patient dies (Danielsen after Klingmüller)⁹⁴⁹

Lepra mixta combines features of both types. It is in some regions more common than the tuberculous or nervous forms.

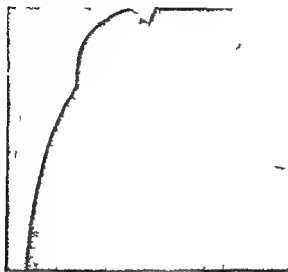


Fig. 141.—Leprosy Nutritional (Courtesy Dr. E. R. Illenberg)

Tuberculoid Leprosy (J. Jadassohn⁹⁴)—Besides the lesions of lepromatous and neural leprosy one may encounter round or gyrate flat smooth slightly discolored skin lesions which may be large or small. The center is usually depressed and the edge slightly raised. Often especially in the edge small lupoid soft nodules can be demonstrated which under the pressure of glass leave a yellowish spot. These show little resistance to piercing with a bulbous probe. Anesthesia is not very marked but some authors found tuberculoid lesions very frequently in the neural type (Lowe et al. after Wilcocks⁹⁵ Ota and Sato after Klingmüller⁹⁴⁹). Some of these cases have sarcoid features⁹⁴⁶. It seems to be quite certain that tuberculoid leprosy does not occur together with lepromatous⁹⁴³ at least this combination must be very rare. Tuberculoid leprosy is of greater theoretical than clinical importance because its tuberculoid structure and purity of bacilli demonstrate the so called law of J. Jadassohn and Lewandowsky according to which tuberculoid structures are apt to appear where microorganisms or their products are destroyed by the local immune biologic reactions (see page 180)*. In other words the immune biologic defenses in tuberculoid leprosy are excellent which is in line with its relatively benign course (see also lepromin reaction).

These cases are generally rare though quite frequent in some small localities. They are more often seen in the Negro⁹⁴⁵.

⁹⁴⁹Sulzberger reviewed formalin with omission of the word rapidly since relatively slow destruction seems likely to produce tuberculoid structures.

⁹⁵Wilcocks Summary of Recent Abstracts (Leprosy) Trop. Dis. Bull. 40: 809-815, 1943.

⁹⁴⁶Klingmüller All recent Abstracts in Tuberculoid Leprosy Klin. Wchnschr. 19: 209-307, 1940.

Mucosal Manifestations —

The mucosae of the upper air passages are in almost all cases involved though in widely varying degree.⁸⁶⁴ The *nose* though rarely affected in neural leprosy has been found involved in the lepromatous variety in 33 to 96 per cent according to a great number of authors from many countries. The nasal mucosa is often the first site of lepromatous lesions and bacilli can often be found in the



FIG 11. Tubercle in pro py (Courtesy L. & M. in Hospital Carall La.)

nasal discharge when no other symptoms exist. The vestibule which may be filled with crusts which have formed over ulcerating lepromas in the nasal mucosa proper is often the site of the same equivalence of changes which takes place on the skin i.e. inflammation infiltration ulceration and crusting. The infiltrates appear as tough yellowish pink pinhead to cherry stone sized granulations which soften and ulcerate quicker than the corresponding skin lesions. The place to look for the lesions is the cartilaginous septum the vestibule and the lower turbinates. Perforation of the nasal septum occurs in about 40 per cent of all types.

Oral infiltrations consisting of grouped small yellowish pink nodules are often found on the *palate*. The pharyngeal reflex is lacking in 60 per cent

⁸⁶⁴ Pinkerton E. J. Leprosy. Upper Respiratory Tract. Texts Laryng. Otol. & Rhin. A.M.A. pp. 97-118. 1939.

of the neural cases (Belowdon after Klingmüller²⁴⁹) Scarring results in deviations of the uvula The gums the tonsils and the labial mucosa are less often involved The lips become more often affected in the skin and vermillion parts than in the mucosa proper



Fig. 143.—Leprosy. Lepromas of the palate. (Court & U. S. Marine Hospital, Cayman, Ia.)

On the *tongue* lepromatous lesions occur as flat yellowish or silvery glossy or tendinous discoid polygonal or streaky nodules or as diffuse infiltrations of the base of the tongue Generally the tongue resists the lepromatous involvement longer than other parts of the mouth The incidence of leprosy of the tongue given in various statistics from different countries varies from 5 to 50 per cent The same type of conglomerations of yellowish pink granulations as are found in the oral cavity occurs on the epiglottis and in the arytenoid area while the vocal cord usually resists for a long time The trachea is rarely affected and if so in the uppermost part

The *lungs* may become lepromatous but this is relatively rare

The *eye* is very often affected in Norway in almost 100 per cent of the lepromatous and in 60 per cent of the neural cases The percentages of other countries are smaller but still considerable Lepromatous involvement of the lids madarosis specific conjunctivitis ectropion keratitis iritis episcleral lepromas lagophthalmus and its sequelae muscular disorders atrophy of bulb and many other lesions are well known²⁵⁰

The *auricle* especially the earlobe is a common site of lepromas while the ear duct usually stays free The internal ear is hardly ever affected

The *sebaceous glands* seem to be more active so that the skin over the lepromas is oilier than normal On this phenomenon was based the medieval water test If the skin did not become wet from water the patient was assumed to be a leper

Perspiration may within the affected areas be increased in the early stages and then paralyzed. The loss of perspiration may be due to specific destruction of the sweat glands or to nervous disturbance.

The *hair* of the body and the beard may early become dry, brittle and thin. The early loss of the lateral third of the eyebrows has often been emphasized. The hair of the head is as a rule surprisingly resistant even in advanced cases but is lost in the affected areas.

Heller¹⁵³ in his monograph on the diseases of the *nails* reports thinning, longitudinal grooves and shedding. Occasionally the nails withstand the advance of the disease surprisingly well so that normal nails can be seen on severely affected fingers of mutilated hands. Complete and permanent loss or reduction of the nails to tiny horny cones are characteristic of the terminal stages.

Pathological Histology—There are three types of pathological changes caused by the leprosy bacillus: the infective granuloma, the nonspecific inflammation and the tuberculoid structures (Lewandowsky after Klingmüller)¹⁴⁹. Furthermore the Hansen bacillus may be found in tissues without causing any changes. The *lepromatous* changes start most often in the walls of the vascular plexus surrounding the follicles, the arrectores pilorum, the sweat glands, the central vessels of the papillae and the cutaneous nerves. These early localizations are indicative of a hematogenous infection. The infective granuloma consists of lymphocytes, plasma cells, epithelioid cells and giant cells. Usually the lepromas contain great numbers of bacilli arranged in bundles or loose groups between the cells in the capillaries of the papillae, in the lymphatics and in round, dense intracellular conglomerations in the cells which are known as globi. Globi often contain more bacillary granula than rods and may become large enough to be macroscopically visible. The intracellular bacilli are mostly found in the lepra cells which are large polynuclear cells with a foamy protoplasm. The lepra cells stem from histiocytes and as such they are part of the reticulo-endothelial system. Their protoplasm is rich in lipids. Before the leproma invades the epidermis it stays for a certain period separated from it by a characteristic leprosy-free layer of tissue, a phenomenon which A. Neisser had observed.

Neural leprosy is characterized by interstitial neuritis. Absence of granuloma formation is striking. The histology of *tuberculoid leprosy* resembles that of Boeck's sarcoid. The lesions consist of sharply bordered perivascular granulomas, sometimes with a necrotic caseating center. Plasma cells are scarce, epithelioid cells abundant. Giant cells of the Langhans type complete the tuberculoid picture. Frazier¹⁵⁴ says that the most typical tubercles of the skin are found not in tuberculosis but in leprosy.

The invasion of the nerves may be metastatic and hematogenous or contiguous from the skin. The latter is very common and explains the predominance of very peripheral neural changes in sensory nerves over motor paralyses.

Tests and Diagnosis—Allergic and serologic reactions have not become as important in the diagnosis of leprosy as in other diseases. In advanced cases the Wassermann and Kahn reactions are often positive. While many

believe that these are nonspecific reactions some more recent investigators (Gundersen Ole Berner after Fellner^{959 960}) believe that a positive Wassermann in a leper means syphilis

*Rubino's*⁹⁶⁵ reaction based on the sedimentation and agglutination of prepared mutton erythrocytes with the test serum is negative in nonlepers^{966 969} often positive in lepers (especially in the tuberculous form)

Some lepers react to *tuberculin* probably without being tuberculous. The serum of nontuberculous lepers may give a positive complement fixation test for tuberculosis. These occasional difficulties are further increased by the frequent tuberculous infection of advanced lepers^{948 969} (Babes after J. Jadassohn⁹⁴⁸)

The serum of lepers is highly toxic to growing young plants⁹⁷⁰ in contrast to the serum of patients with syphilis or tuberculosis

Allergic skin reactions with allergens derived from *lepromas* have become important^{971 97}. Silent immunization in leprous surroundings and anergy must be considered in the interpretation

The *Mitsuda*⁹⁷¹ reaction is not so much used to establish the diagnosis of leprosy as to test the immune biologic defense of a patient in order to gain a basis for prognosis. The test consists of the intracutaneous injection of 0.1 c.c. of lepromin, an extract from lepromas⁹⁸¹. If the reaction is positive a papule develops in the second week. It reaches its acme in the fourth week with a nodule $\frac{1}{2}$ — 1 cm. in diameter which eventually may ulcerate and slowly heal. The papule has a tuberculoid structure. The test is often positive in healthy persons from leprous surroundings and in tuberculoid leprosy; it is often negative in lepromatous leprosy and doubtful in cases with histologically nonspecific inflammatory lesions. The negative lepromin reaction in lepromatous leprosy with abundant bacilli is explained by a lack of defense to the infection and is therefore considered a bad prognostic sign. The positive reaction is considered as an indication of vigorous defense and relatively favorable prognosis (see tuberculoid leprosy and law of Jadassohn and Lewandowski pp. 180 and 242).

Febrile and focal reactions to 0.2 to 3.0 grams of *potassium iodide* or to intravenous injections of sodium iodide occur frequently in lepers and have diagnostic value. The serologic reactions may become activated and the increased nasal secretion may lead to the detection of leprosy bacilli in smears

⁹⁵⁹Rubino M. C. "Micro-diagnostic de la lèpre par l'agglutino-sédimentation des globules rouges de mouton formolés" Bull. Acad. de méd. Paris 105: 890-893, 1931 also Ann. Int. Fa. sur 47: 147, 172, 1931.

⁹⁶⁶Lépin I. Markianos and Panayotou A. "Valeur pratique de la réaction de Mitsuda pour le séro-diagnostic de la lèpre" Bull. Soc. path. exot. 25: 443, 1931, Zbl. 43: 407.

⁹⁶⁷Hombria M. "Zum serologischen Studium der Lepra" Acta dermat. ven. 23: 193, 200, 1937, Zbl. 44: 634.

⁹⁶⁸Montanes P. "Diagnostischer Wert der Mitsuda'schen Reaktion bei Lepra" Acta dermat. ven. 23: 241, 267, 1937, Zbl. 44: 540.

⁹⁶⁹Brant J. "Erythrocyte sinking action bei Lepra" Latv. arsts. žurnāls 11: 619-63, 1932, Zbl. 44: 33, 1933.

⁹⁷⁰Nacht E. J. "Phytopharmacological studies on the effect of myoglobin, syzillin and leproy" Acta dermat. syph. 18: 176-137, 1937.

⁹⁷¹Mitsuda K. "Tribute to the International Conference of the Leprosy Commission and Hygiene" Paris 1934, J. B. Baillière et fils.

⁹⁸¹Harsh P. "Hautreaktion bei Lepra" Ztschr. f. klin. med. Forsch. u. therap. 47: 529-531, 1926.

which were previously negative. *Biopsy* of the skin or nasal mucosa, testing of the serum of blisters produced by carbon dioxide snow and puncture of lymphatic nodes are some of the laboratory methods successfully used to find bacilli. For the preparation of *nasal smears* the mucosa should be gently scraped without causing bleeding.

Clinical similarity to a great number of dermatoses may develop in one or the other stages of this chronic disease. Psoriasis, ichthyosis, mycosis fungoides, leukemia, blastomycosis, syphilis, lupus erythematosus, vitiligo and a number of other skin diseases may occasionally be suggested by atypical leprosy.

The course, the occurrence of leprosy in the surrounding region, macules and lepromas, biopsy and above all anesthesia will usually decide the question. If the cooperation of the patient in testing of the sensory functions is lacking, the histamine test may prove valuable. The skin is pricked with a needle through a drop of histamine salt solution 1 — 1000. In paralysis of the sensitive nerve endings a wheel appears as in the normal skin but it lacks the red areola which is normally seen. This is called a negative histamine test. Pardo Castello and Tiant⁶⁴ found this test negative in the cutaneous lesions of leprosy. The most difficult problems however may arise from nervous diseases and particularly from syringomyelia. Here the anesthesia is more sharply bordered and the muscular atrophy (which in leprosy is usually restricted to the anesthetic parts of the hands) affects the arms and shoulders. Scoliosis, bulbar symptoms, pathological fractures of the long bones, ataxia, central unilateral facial paralysis, tremor, spasms—in short central neurologic symptoms and signs—are more suggestive of syringomyelia. The neural phenomena of leprosy are usually of peripheral character.

Treatment—No specific therapy is known. The derivatives of the *chaufmoogia* oils which are obtained from several tropical trees are so far the most effective drugs. Recently, promin, a sulfone derivative has given encouraging results.⁶⁷

⁶⁴Tagliacozzi, P. and R. C. J. ha. J. P. A. Dinan. J. E. P. Jan. B. N. and Fr. Jan. C. O. J. om. Tr. im. t. of J. r. x. l. u. J. l. i. h. R. p. 68. 1772. 1741. 1913.

CHAPTER XIII

DERMADROMES OF INTOXICATIONS

A poison may cause a dermatosis by external contact without systemic interference (discolorations by dyes necroses by caustics) or by damaging the skin as part of the damage to the entire system. In the latter case one must separate the intoxications in the strict sense from the allergic reactions. In *intoxications* the causative agent is toxic to all individuals if it is absorbed in a certain dose the damage it produces depends on the nature the amount and concentration of the poison and also on the length of time it acts excessive doses being lethal. The poison can be excreted and antidotes may reverse the process. There is no incubation period and the agent may be found in the tissues by chemical analysis. These are some of the features characterizing intoxication in contrast to allergy (Tzanck after R. L. Mayer⁹⁷⁴).

Thallium alopecia and argyria are examples of this sometimes called classical type of toxidermia.

In the case of *allergic reactions* a specific alteration in the capacity to react acquired by previous exposure to the agent⁹⁷⁵ is the dominant pathogenetic factor though the nature and dose of the poison (allergen) should not be underrated. The allergic dermatoses have been the subject of several recent monographs^{976, 978} and their character as a manifestation of internal disorders is not yet clearly enough understood to warrant more than a short mention in this book. The dermatoses caused by metabolic and bacterial toxins are being dealt with in other chapters. Thus only the *skin manifestations of systemic poisonings* in the strict sense of the term shall be discussed in the following chapter.

Arsenicals

Arsenical poisoning occurs in a great variety of circumstances. It is an industrial hazard in the mining and smelting of many ores especially gold and copper. The gases from the copper furnaces the commercial metal sulfides as well as sulfuric acid are often contaminated with arsenic. Lead arsenite calcium arsenite and Paris green are rat poisons and agricultural insecticides used on such important crops as cotton tobacco apples grapes and vegetables⁹⁷⁷. Several arsenites sulfides of arsenic and other compounds are bright colored pigments which in spite of modern paints and legislation have been and probably still are in occasional use in wall prints wall papers toys and colored papers.

Medical administration of arsenicals is a common cause of arsenicism. Suicidal and homicidal attempts and laboratory and industrial accidents are

⁹⁷⁴Mayer R. L. *Toxicodermis* in *Handbook of Dermatology* 4: 2: 1252 1933

⁹⁷⁵Sulzberg M. B. *Dermatologic Allergy* Springfield Ill 1940 Charles E. Thomas

⁹⁷⁶Eachus P. *Allergy* New York 1934 Grune & Stratton

⁹⁷⁷Ayres Jr. and Anderson N. P. *Cutaneous Manifestation of Arsenic Poisoning* Arch Dermatol & Syph 36: 33-43 1934

relatively rare by comparison. Mass poisonings affecting many thousands of people and remaining unexplained for a long time have occurred in a great number of instances. Such a so called epidemic terrified Paris in the 1830's. About 40 000 persons became victims of a disease then called acrodynia which later was identified as arsenic poisoning. In later epidemics the cause was established by means of modern chemistry. There were several mass poisonings by wine from vineyards where arsenicals had been used for spraying. The last one occurred on ocean liners in 1932.^{978 979}

In 1900 sulfuric acid containing arsenic used in converting cane sugar into invert sugar for beer brewing in England caused one of the greatest mass poisonings in history. Drinking water contains arsenic in toxic amounts (more than 0.2 mg per 1000 cc) in many localities (Kathe after R. L. Mayer⁹⁷⁴). Chronic skin manifestations are likely to be found among the inhabitants as was shown in the description of the drinking water epidemic in the little Silesian mining town of Reichenstein.

The descriptions of these epidemics (partly given by such masters of dermatology as Vidal Barthélemy and A. Neisser and their schools) laid the foundations of our present knowledge of arsenical intoxication which is one of the best studied of all human poisonings.

Acute arsenical poisoning is characterized by severe gastrointestinal symptoms which resemble cholera and may cause death in a short time often after a few hours. Excessive lacrimation and salivation are early manifestations.

Within a few days or a week polyneuritis with multiple paralyses may develop together with cutaneous symptoms and may last a long time. Formication pruritus numbness wrist drop and tabes like syndromes are characteristic neurologic symptoms. There exist a great variety of clinical pictures e.g. psychoses and agranulocytosis but nervous and cutaneous symptoms are significant if not the dominating features of the subacute and chronic cases.

The diagnosis of arsenic poisoning⁹⁷⁷ depends on the history, clinical appearance and the presence of arsenic in the urine or hair in an amount which is decidedly above or a multiple of the value which may occur under normal conditions. Geographic location drinking water peculiarities of the soil or a diet rich in seafood which may contain as much as 8 mg per kilogram are factors which must be considered. Representative normal figures have been stated as 9.7 mg per hundred grams substance for the hair and skin 17.2 mg for the nails and 10.4 mg for the urine.⁹⁸⁰ Wilcox⁹⁸¹ and Ayres and Anderson⁹⁷⁷ recommend the Guthzeit test for urinary analysis which is a relatively simple color test.⁹⁸²

⁹⁷⁸Thorel and Vézient. A propos d'un Intoxication collective par l'arsenic. J. Agr. H. d. r. m. t. et Hyg. 2: 614-6 1903.

⁹⁷⁹Mohl. J. Leber. I. Mause. ergiftung nach Weinussanborl. D. tech. med. Wehnachr. 103: 1 8-1-1 5.

⁹⁸⁰Bull. t. r. O. and Marfurt. De la t. ur no male en arse. le d'arsenic. corps humain. Il. l'et. chim. acta 2: 10-14 1923.

⁹⁸¹Wilcox. W. Acute Arsenical Poisoning. Tr. Med. Leg. Soc. Lo. 1 22: 149-157 1930.

⁹⁸²Aut. l. th. W. H. section. f. l'ind. ed. 4 Philadelphia 1915. P. Blakiston & Son & Co.

Sometimes it is possible to demonstrate arsenic in the biopsy specimen of skin lesions.^{983, 984} A progressive diminution of arsenic in the urine with clinical improvement under sodium thiosulfate therapy and the recurrence of symptoms on exposure to arsenic would be further proof. A positive patch test would show that there has been enough exposure to arsenic to produce sensitization.

Dermadromes—The earliest skin manifestation of arsenical poisoning is *pruritus* which in some cases is restricted to the palms and soles. Conjunctivitis corvæ and *puffiness of the eyelids* are also early warning signals which are observed more often in the course of prolonged arsenical treatment than after acute poisonings with one large dose. Other frequent and early symptoms are dis-

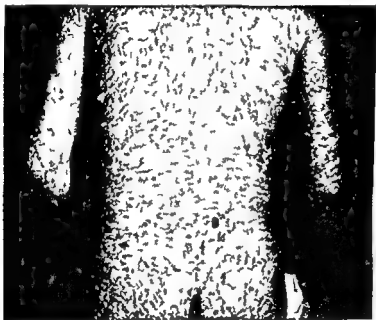


Fig. 144.—Exfoliative dermatitis (erythroderma) following arsenic poisoning. (Courtesy Dr. Carleton Cooper.)

tinctly bordered *palmar and plantar erythemas*. Their diagnostic importance is great because of the ease with which they can be noticed in ambulatory patients under continual arsenic treatment. The accumulation in the sweat glands which concentrate and eliminate the arsenic (Hutchinson after Ullman⁹⁸⁵) as well as the arsenophile keratotic epidermis are responsible for the site of the erythemas. *Palmar plantar sweating* is known as an early symptom.⁹⁸⁶

⁹⁸³Osborne J. D. Microchemical Studies of Arsenic in Arsenical Dermatitis. *Arch. Dermat. & Syph.* 18: 37, 1927.

⁹⁸⁴Osborne J. D. Microchemical Studies of Arsenic in Arsenical Dermatitis. *Arch. Dermat. & Syph.* 12: 773, 1928.

⁹⁸⁵Ullman H. Über Arsen in der Haut. *Arch. Dermat. & Syph.* 15: 49, 1911.

⁹⁸⁶Simon R. D. J. Skin Manifestations in Arsenic Poisoning. *N. Engl. J. Med.* 193: 5367-5368, 1935. *Zbl.* 83: 19.

Widespread or even truly generalized rashes following the intake of arsenicals may be seen together with or following the palmar plantar erythemas

Scarlatiniform morbilliform and *erysipeloid* erythemas are also known. Of greatest importance are the *eczematoid eruptions* which if further intake of arsenicals is not halted may rapidly develop into generalized exfoliative dermatitis which is such a great hazard in the use of the arsphenamines (see there) while it is rarely provoked by the inorganic arsenicals

Generalized rashes may also be urticarial vesicular or bullous. K Ullmann⁸⁸⁷ emphasizes the sequence of pruritus urticaria and edema followed by circumscribed and later generalized erythemas

The generalized exanthems may also appear as large or small scaly patches in some instances resembling *psoriasis rosea* or *parapsoriasis*. Older lesions of this kind may have a heavier covering with scales and thus imitate *psoriasis* closely. The arsenical erythema may also surround and accentuate pre-existing psoriatic lesions.⁸⁷⁴

The eruptions sometimes imitate *lichen planus*. This is a remarkable fact with regard to the great efficacy of arsenic in lichen planus. No generally accepted explanation for this clinical coincidence has been offered and cannot be expected before more about the etiology of lichen planus is known

Scleroderma as a probable arsenical sequel^{888 889} has been observed in a considerable number of instances. Generalized *poikiloderma* as a permanent damage after arsenical dermatitis is also on the long list of rare arsenical arsphenamine reactions.⁸⁹⁰ Recently nine cases of *acrodermatitis chronica atrophicans* have been observed in a group of wine growers affected with occupational arsenicism.⁸⁹¹

Edema is a common symptom in arsenical eruptions. There may be only slight puffiness of the eyelids and cheeks but generalized edema is hardly ever absent in the severe forms of dermatitis

Petechiae and other hemorrhagic symptoms are of rather grave prognostic significance.⁸⁸ *Herpes zoster* is reported to occur in 18%⁸⁹² or even 10 to 20 per cent⁸⁹³ of the cases. The high incidence of herpes zoster in the English beer epidemic was one of the facts which pointed to arsenic as the causative factor

Pustules ulcers necroses and perforations of the *nasal septum* are caused by the local external caustic effect of the arsenic

The *oral mucosa* may participate early in the toxic syndrome with pharyngitis and gingivitis. Ulcerative stomatitis or glossitis may occur in severe cases

- ⁸⁸⁷ Ullmann J. *Ars nigratos und Ar schwarzenbildung* Zbl 35 314 1931
⁸⁸⁸ Ayres S Jr. *Scleroderma a Possible Manifestation of Chronic Arsenic Poisoning* Arch Dermat & Syph 2 4 1920
⁸⁸⁹ Ayres S Jr. *A Fifth Case of Scleroderma With Arsenic in the Urine* Arch Dermat & Syph 2 15-17 1911
⁸⁹⁰ Cason A B. *Jaundice and Arsenic Poisoning* J. I. Fisher J. I. *Toxicodermatologic Changes in Skin Following Arsenic and Bismuth* J. A. M. 218 1 199 1942
⁸⁹¹ Hienkema H. *A red nodules in the atrophic an* bei Winkeln mit Arsen schädigungen Arch f D mat u Syph 279 61 0 1933
⁸⁹² L. H. *Herpes zoster während Arsenik* Monatsh f prakt Dermat 21 307 1900
⁸⁹³ Ceylan L. *Herpes zoster Haut* A. I. ru. g. n. beim Arsenikismus und Betrachtungen über die Massenkrankung n. R. J. h. t. in d. S. h. d. n. Arch f D mat u Syph 43 2 1 1898

The *hair* is almost always diffusely shed. The alopecia is complete in severe cases of arsenical dermatitis.

The *nails* usually record severe dermatitis as well as acute especially single dose poisonings by cross furrows (Beau's lines) or with white⁵⁵ or gray cross lines. The latter have become known as Mees' bands^{56, 57} and are often associated with polyneuritis arsenicosa. They are dull glistening bands extending across the breadth of each finger nail. The bands appear at the lunula about eight weeks after the poisoning. If one adds 10 days for every 1.1 — 1.2 mm of the distance from the proximal border of the lunula to the distal border of a band one can determine the approximate date of the poisoning. The arsenic content of a band has been found to be 10 times higher than in the undischored parts of the nails.⁵⁸

The condition is apparently identical or similar to the *leukonychia striata* which was observed in many instances during the English beer epidemic and in other instances of arsenical poisoning. The nails may be shed after severe arsenical dermatitis.

Arsenical dermatitis of all types heals with *hyperpigmentation* of varying intensity which may even develop without preceding noticeable inflammation.

The distribution, depth and duration of the hyperpigmentation vary within wide limits. The areas which have a natural tendency to darken such as the genitals, groins, umbilicus and mammillae as well as scars, healing skin lesions and pressure and friction points are often highly pigmented.⁵⁶

The individual tendency to pigment has a much greater influence on the melanosis than the size of the doses of arsenic. Melanosis may appear as early as 12 days after the onset of arsenical medication and after small doses. On the other hand severe poisoning may fail to produce it. This is well demonstrated by the fact that in poisoning from drinking water with generally equal supply to the population only some persons develop marked melanosis. The discoloration may start insidiously and reach any even the severest degree.⁵⁹

The diffuse type of arsenical melanosis is so similar to the appearance of Addison's disease that during the great beer epidemic in England most cases were so diagnosed until the autopsies failed to reveal adrenal changes. The covered parts of the skin seem to darken more than the open ones⁶⁰ although the face is frequently affected. In a minority of the cases a dense regularly reticulated or dappled pattern of pigmentation and depigmentation may cover wide areas especially the back. This type of arsenical melanosis has been called *raindrop pigmentation* because of its resemblance to a window pane covered with raindrops. This characteristic type of arsenical pigmentation is often found in chronic arsenicism due to drinking water or prolonged administration of inorganic arsenicals.

⁵⁵Mees H. A. E. verschijn. i. bij polyn. uriti. arsenicosa. Ned. i. tijdschr. v. Geneesk. 1919 I 391-396.

⁵⁶Bark L. F. E. foliati o D. rmatiti. In Accidental As. Poisoni. g. Mees Band I. Urol. & Cutan. H. v. 46. 57. 1927. 1942.

⁵⁷Wigand R. Das Mees'sche Nagelband bei Ecl. yn. uriti. arsenicosa. Mün. i. med. W. 1. 1927. 53. 834. 1940.

⁵⁸Thron. H. Arsenical Pigmentation. Arch. Dermat. & Syph. 24 479. 1931.



Fig. 145 Arsenical melanosis: rain drop appearance. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

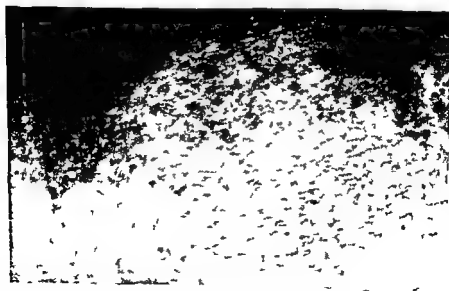


Fig. 146 — Arsenical melanosis: rain drop appearance.

Arsenical melanosis has also been seen to follow the pattern of underlying large veins.⁹⁷⁸

The *depigmenting* tendency after arsenical dermatitis is best observed in Negroes⁹⁹³

In rare instances the *oral mucosa* participates in the pigmentation, although the lack of oral pigmentation has often been emphasized as a differential criterion against Addison's disease. The arsenical melanosia may vanish rapidly with the other symptoms of the intoxication but more often it persists much longer or even permanently.

The arsenical pigment is *melanin*⁹⁹⁹ and as such is iron free - It can be distinguished from arsenic crystals⁹⁸⁴ which lie mostly between the cells



Fig. 147 —Arsenic alkal ratios of palm after indurinate us of Fowler's solution in p o la le

Keratoses are the most common and characteristic and the most easily detectable of all skin manifestations of chronic arsenic poisoning

The keratoses may appear within a few weeks after the start of arsenic intake or as late as many years after the medication or other exposure has been stopped.¹⁰⁰⁰ An erythema may or may not precede their appearance.

The characteristic sites of the hyperkeratoses are the palms and soles with their peculiar affinity for arsenic. The areas of friction and pressure which normally tend to callus formation are especially apt to develop arsenical hyper-

¹²Cannon A B and Farellitz M B Vitiligo From A Iridinamin De matitia and From Arsenic Arch Dermat & Syph 28 647-651 1933

1915 ¹⁹¹⁷Can O III tologie r Arz m La o e H ltr s path Anat u x allg lath 80 ° 2-38

1915
1000 Montgomery H. Arsenic as an Etiologic Agent in Certain Types of Epithelioma Arch
Dermat & Syph 32 18 236 1935

keratoses. Thus the plantar arch and the center of the palms remain relatively free from circumscribed lesions but they are not immune against diffuse keratosis. Occasionally circumscribed keratoses may appear on the back on the chest on the extensor surfaces of the elbows and knees on the heels or on the dorsal of the hands and feet.^{1000 1001}

Hyperkeratoses may be diffuse and cover the entire palms and soles. Much more characteristic however are the circumscribed lesions. They are often called warts but they are less circumscribed and vascular than ordinary warts. They are cornlike accumulations of horny tissue and because of their completely epidermal structure they are more transparent than warts or corns. Their color is usually pale yellow but thicker layers may take on a dirty gray or even slate or brown hue. The opening of a sweat gland is sometimes visible at the top of a small lesion. The size varies from that of a millet seed to a pea or even an almond. *Hyperidrosis* is a frequent annoying accompaniment which may even be the preëminent symptom in cases of arsenical keratosis.



Fig. 145.—Transition of arsenical keratosis into a wart.

There exists only a very rough parallel between the appearance of the keratoses and the dose and length of time of arsenical exposure. Examples of extensive keratoses after small amount of arsenic and complete lack of keratoses after huge doses are well known.¹⁰⁰⁰

Chronic intoxication with inorganic arsenicals is especially apt to cause keratoses while they are rarely seen among the tremendous numbers of people treated with triphenylamines. The circumscribed keratoses usually disappear

¹⁰⁰⁰Kumler L. Mächtigkeit pupillmässiger Wucherungen auf der Haut. Zf. 28 810 1906.

PLATE II

- 1 Lupus erythematosus acutus · Rapidly fatal case
- 2 Arsenical keratosis with carcinoma
- 3 Leaking aneurysm of the abdominal aorta · Giant ecchymose
- 4 Hypertension · Chronic nephritis · Irriginous eruption
- 5 Vagabonds' skin
- 6 Erythema palmare · Mitral insufficiency



gradually with the elimination of the arsenic. Sometimes however they are permanent. If they are removed they grow back rapidly. Such keratoses of many years standing are *precancerous* lesions.

Montgomery¹⁰⁰⁸ saw *epitheliomas* develop in 20 per cent of his 85 cases of arsenical keratosis but the percentage is likely to be smaller in less preselected material than is encountered at the Mayo Clinic.

The cancers are usually of the squamous cell type. Some assume features of Bowen's disease by the formation of grouped or circinate lenticular, crusty or scaly papules. But it has not been sufficiently proved that Bowen's disease and superficial epitheliomatosis generally are due to arsenic as had been suggested¹⁰⁰⁹. Arsenical epitheliomas may also appear independently of keratoses. They may occasionally look like superficial epitheliomatosis forming thin scaly plaques which however often lack the thin threadlike pearly border of this variety of skin cancer.¹⁰⁰⁹



Fig. 149 — Arsenical keratosis resembling Bowen's disease

Basal cell epithelioma is very rare. The degree of malignancy is relatively low, metastases occurring very late. Arsenical cancers of the urethra, bladder and bronchi have been observed in rare instances.¹⁰⁰³

The cancers are not very malignant. They metastasize late and are seldom and only after a long time destructive. They respond well to radiation and even the excision of relatively large cancers may be successful. In all cases of

¹⁰⁰⁸Anderson N. P. Bowen's Precancerous Dermatoses Benign Superficial Epitheliomas Arch. Dermat. & Syph. 28: 10, 193.

¹⁰⁰⁹Goeckerman W. H. and Wilkin L. F. Arsenic as Cause of Cancer of Mucous Membranes Arch. Dermat. & Syph. 42: 641-644, 1940.



Fig. 150 — Large arsenical cancer over Achilles tendon. Indiscriminate use of Fowler's solution against pyoderma.

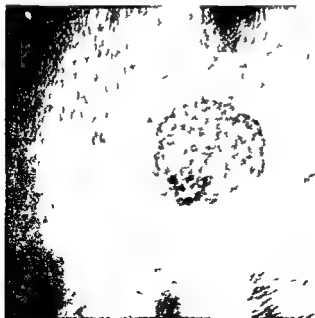


Fig. 151 — Superficial pythiomatosis in a patient with arsenical dermatoses and a history of indiscriminate use of Fowler's solution.

multiple epitheliomas of the skin the possibility of an arsenical etiology should be considered ^{1000 1001}

Arsenical keratoses should be treated by any superficially destructive measure such as dry ice fulguration etc. The use of keratolytic salves gives only temporary results. The value of sodium thiosulfate medication either by the intravenous injection of 1 gram daily or by mouth is controversial.

Arsenical epitheliomas should be treated like other skin cancers.

Arsphenamines—The dermatoses due to the use of arsphenamines are either arsenical in character or they are specific allergic phenomena ¹⁰⁰⁴

The *angioneurotic syndrome* or nitritoid reaction occurs immediately after an intravenous injection of any one of the arsphenamines, particularly if the injection has been given at a fast rate.

Itching may be the first symptom of this reaction but it is quickly followed by a feeling of great congestion and pressure in the head, dyspnea, palpitation and anxiety. There is acute redness of the face as if the patient had inhaled amyl nitrite. The face may become acutely swollen. Soon the bright erythema becomes cyanotic and in severe cases the patient may become unconscious and the breathing stertorous. The terrifying episode is usually over after a few minutes especially if adrenalin is injected. Death has rarely occurred. An exceedingly slow rate of injection, change of the type of arsphenamine and lowering of the dose are the best means of *pre-ention*.

Urticarial or in rare instances bullous rashes appearing in the same site immediately or shortly after the injection are called *fixed arsphenamine eruptions*.

The severest cutaneous disease following the administration of any one member of the arsphenamine group is *generalized exfoliative dermatitis*. This dangerous dermadrome usually starts after several injections have been given or not infrequently a few weeks after the series of injections has been finished.

Fever, anorexia and slight erythema often precede the main rash which appears first on the extensor aspects of the knees and elbows as a morbilliform or carlatiniform eruption. Within a week it develops into generalized acute erythroderma. There is usually widespread or even generalized weeping edema, fever, albuminuria and hepatitis. Septic symptoms especially multiple boils and foci of cellulitis and necrosis are a prominent feature. This may last for many weeks. Gradually the skin dries up and is exfoliated in large sheets especially about the hands and feet. Melanosis of moderate degree follows frequently. There is always diffuse effluvium of the hair and often the entire hair falls out. The nails may also be shed. The prognosis is most dubious. Death from sepsis occurs frequently.

A large recent American series gives the incidence of severe crustaceous dermatitis as 0.7 per 1000 injections. The patients were not previously treated with arsphenamine ¹⁰⁰⁵. This seems much higher than other observations.

¹⁰⁰⁴Birnbaum H. *Salvarsan-schädigung n der Haut* Zbl 49 II 106 1936

¹⁰⁰⁵Waugh J H and Milovich F. *Fever Reaction to Arsphenamine Among 300 Patients Previously Treated With It* Dis Inform 21 349-394 1940

Allergy to arsphenamines in cases of dermatitis has often been demonstrated by positive patch tests¹⁰⁰⁶. Women were twice as often affected as men¹⁰⁰⁵.

The treatment requires daily injections of 1 gram of sodium thiosulfate and best nursing care. Penicillin is probably helpful in combating pyogenic infection. Liver extract has often been recommended.

Convalescents should not be subjected to any further arsenical treatment.

Early acute arsenical erythema or *erythema of the ninth day* is a febrile multiform rash of unknown etiology occurring in about 3 per cent of the patients treated for the first time with trivalent arsenicals¹⁰⁰⁷. The rash is described as generalized and composed of irregularly macular or morbilliform lesions clearing up after 2 days. Arsenical treatment may be continued with extreme caution only but is better replaced by penicillin¹⁰⁰⁸.

Other rare eruptions following the use of arsphenamines include *lichen planus* and *lichen spinulosus*¹⁰⁰⁹. Jaundice is a frequent after effect of arsphenamine treatment. There is no consensus whether arsphenamine alone, allergy, syphilis, another infection or a combination of factors are responsible for the frequent cases of hepatic disease in the course of antisyphilitic treatment with neoarsphenamine¹⁰¹⁰.

Gold

Gold poisoning is almost exclusively due to medication, gold sodium thio sulfate (sancrocylin) being the most widely used compound. The general symptoms follow the pattern of other heavy metal intoxications including arsenic. There may be nephritis, enteritis, hepatitis and a depression of the hematopoietic system in severe cases ending in agranulocytosis or aplastic anemia.

Ill effects mostly of a mild nature were estimated to occur in about 10 per cent of 1400 tuberculous patients treated with gold compounds¹⁰¹¹. They were much more common in the early days of gold therapy when high doses were advocated.

Dermadromes—The skin is most often affected¹⁰¹. The injection of a gold salt even in small quantity may cause immediate or early *nitritoid reactions* with a flushed face and a sensation of giddiness, sometimes with severe cervical pain. Such reactions occurred most frequently after sodium thiomalate (myochrysin)^{1012, 1014}. They are very rare after gold sodium thiosulfate if it is injected slowly into the vein.

¹⁰⁰⁶Schoch A. ■ The Patch Test and the Element of Syringe Contamination in Arsenamine Sensitization Dermatitis. J A M A 98: 1367, 1931.

¹⁰⁰⁷Cañizares O. and Thomas E. W. Early Acute Arsenical Erythema. Arch. Dermat. u. Syph. 38: 567, 1939.

¹⁰⁰⁸Leifer W. Danger of Continued Arsenotherapy in Cases of Erythema of Ninth Day. Am. J. M. Sc. 210: 458, 1945.

¹⁰⁰⁹Olavsek W. ■ Seltene Salvarsan-echide. Dermat. Wchnschr. 118: 409, 1942.

¹⁰¹⁰Winkler M. Dermatitis and Icterus Following Arsenamine in a Syphilitic. Thromb. Thromb. of Syphilis. Dermatologica 82: 297, 309, 1940.

¹⁰¹¹Mayr O. Gold Treatment of Pulmonary Tuberculosis. Mitt. J. Tuberk. 28: 131, 139, 1934.

¹⁰¹²Fellner M. Die Goldthromb. in der Dermatologie. 711: 43, 37, 1932.

¹⁰¹³Lints R. M. Toxic Reactions With Gold Salts in Treatment of Rheumatoid Arthritis. J. Lab. & Clin. Med. 28: 1679-1684, 1941.

¹⁰¹⁴Nicolas J. Lebeuf P. and Mollard H. Sur quelques accidents infectieux de la chrysothérapie (une crise nitritoid) et de nouvelles localisations tuberculeuses. Bull. Soc. franc. d. dermat. et syph. 39: 874, 876, 1937.

All the familiar types of toxic exanthems have been observed. Morbilliform and scarlatiniform rashes are relatively common; multiform and bullous eruptions are rare.

Some exanthems resemble pityriasis rosea but they lack the primary lesion.¹⁰¹⁵ Itching may be the first symptom of all these rashes and should be reason to discontinue the treatment.



Fig. 15. Acute petechial eruption provoked by gold therapy of chronic lupus erythematosus.

Hemorrhagic eruptions seem to occur more frequently than in arthralgia poisoning.^{9, 1016} The tuberculosis or syphilis of the patients treated with gold may have some importance in the pathogenesis of the purpuric¹⁰¹⁷ mostly petechial rashes. These eruptions are frequently accompanied by other hemorrhagic phenomena, especially hematuria. Naturally all hemorrhagic manifestations are potentially serious. *Generalized exfoliative dermatitis* with loss of hair and nails though rarely with a fatal outcome¹⁰¹⁸ has been observed.^{101, 1019}

Lichen planus like eruptions seem to be a feature of the gold dermatoses.¹⁰²⁰ They may be subacute with violent itching vesicles and blisters or even turn into generalized exfoliative dermatitis. More commonly they consist of relatively

¹ Wilk J. and Courville C. J. Pityriasis-Rosea Like Dermatitis Following Therapy With Myochrysin. Arch. Derm. & Syph. 12: 1105-1111, 1940.

² Emilio-Well J. and Roussier J. Les éruptions hémorragiques post-augmentales. Sa. g. 8: 825-839, 1931.

³ Couget H. and Blum P. Syndrome hémorragique d'origine hépatique tardive en traitement par l'or. Bull. Soc. franç. de dermat. et syph. 40: 877-879, 1933.

⁴ Martini H. Die Behandlung des Lupus erythematosus mit Kryosolgan. Klin. Wchnsch. 1: 35-37, 1922.

⁵ Blumenthal A. J. C. On the treatment of the skin after Gold. Derm. titl. Ned. Tijdschr. v. Geneesk. pp. 2613-2614, 1923. Zbl. 58: 60.

⁶ Villi E. L. Lichen Planus Due to Gold Therapy. Bull. Soc. franç. de dermat. et syph. 46: 38-41, 1939.

large flat papules which have a tendency to coalesce into large plaques of the lichen corneus type ¹⁰⁷¹

There are two kinds of skin *discoloration* known to follow the administration of gold. One is caused by deposits of *melanin* in the upper cutis. This type corresponds to the more common arsenical melanosis and is reversible. It frequently develops after gold rashes ¹⁰⁷² but it may also be primary and occur after small doses ¹⁰⁷³

The second type is of greater and more practical interest. The injected salt is reduced to *metallic gold* and deposited in the lower cutis in the subcutis in the kidneys and in all parts of the reticulo endothelial system.

The visible discoloration is restricted to the skin exposed to light. No difference in the gold content between discolored and apparently normal skin can be found by means of spectroscopic or histologic analysis ¹⁰⁷⁴. With the slit lamp gold particles can be demonstrated in the cornea.

The darkening is diffuse and slate to graphite gray in color. Most observers emphasize a bluish or purplish hue ¹⁰⁷⁵. The dyschromia seems to be permanent. Lorenzen ¹⁰⁷⁶ found that none of his tuberculous patients who had received more than a total of 0.15 Gm. of sodium aurothiosulfate per kg. body weight escaped chrysiasis but none of those with a total of less than 0.05 Gm. per kg. developed it. The trouble becomes visible one to three years after the treatment. Mild cases of *chrysiasis* as this discoloration caused by gold deposits is called do not as a rule constitute a very conspicuous disfigurement.

With the commonly used doses of up to 50 mg. per injection the danger of producing chrysiasis is remote.

Hyperkeratoses and diffuse keratoderma after gold treatment are very rare ^{1077 1078}

Oral symptoms of gold eruptions have frequently been described. Dryness and metallic taste are often the first symptoms of gold intolerance. Simple erythematous or vesicular stomatitis may occur with edema and ulceration of the tongue in severe cases. Gold stomatitis has been seen to precede rashes ¹⁰⁷⁹. Clinically and histologically typical oral lichen planus almost always without accompanying cutaneous lichen planus has been noticed relatively often ^{974 1079 1080} as a sequel of gold intolerance. The lesions are white irregular thin or slightly

¹⁰⁷¹Cougerot Vial and Nekam. Lichen ou prurigo v. ruqueux intenses et très étendu. Bull. Soc. franç. d. dermat. et syph. 43: 1542-155 1936

¹⁰⁷²Zary A. Horowitz A. and Souillard J. Eruption en nappes et acné cornée consécutives à une érythrodermie aiguë. Bull. Soc. franç. de dermat. et syph. 40: 1616-1619 1933

¹⁰⁷³Jergans. Keratolyma and Melanoderma Accompanying Therapy With a Gold Compound. Arch. Dermat. & Syph. 39: 61-623 1937

¹⁰⁷⁴Koch A. G. Chrysiasis. Arch. f. Dermat. u. Syph. 178: 373-379 1938

¹⁰⁷⁵Heimdt O. E. L. Chrysiasis. Arch. Dermat. & Syph. 41: 446-472 1941

¹⁰⁷⁶Lorenzen J. N. Ueber das Entstehen von Chrysiasis im Frühstadium der Natriumaurothiosulfatbehandlung. Lungentuberkulosen. Beitr. z. Klin. i. Teil. rk. 76: 656-657 1931

¹⁰⁷⁷Roxburgh A. C. J. J. A. I. M. d. Gordo. D. Gold Dermatitis With Hyperkeratosis. Brit. J. Dermat. 45: 137-142 1936

¹⁰⁷⁸Journier L. A. B. Boltan. Gold Dermatitis. Rev. de stomatol. 28: 691-696 1935 Zbl. 23: 679

¹⁰⁷⁹Finnrud C. W. Lupus erythematosus der Mundschleimhaut. Arch. f. Dermat. u. Syph. 145: 318-330 1930

¹⁰⁸⁰Mohrmann H. H. U. Lichen planus der Mundschleimhaut nach Goldbehandlung. Dermat. Wchnschr. 99: 1373-1376 1934

popular keratoses of the buccal and labial mucosae¹⁰³¹ They may disappear after discontinuation of the gold treatment

A peculiarity of gold is its activating effect on chronic inflammations and infections especially tuberculous foci The appearance of papulonecrotic tuberculosis under gold treatment has been reported (Medina after Throne et al¹⁰³²)

Silver

While there is little known about acute toxidermia caused by silver this metal is more likely to cause permanent deposits and discolorations than any other metal The *dyschromia* from silver is called *argyria* argyriasis or argyriasis

Occupational argyria has been seen in the chemical industry and among workers who blow a silver nitrate solution into glass beads or Christmas tree decorations to silver the inner surface After many years in this trade such craftsmen sometimes become deep black with a metallic sheen^{1033 1034} Of much greater importance though rarely reaching the same degree of discoloration is the argyria caused by the use of silver compounds in medical therapy

Silver nitrate pills for peptic ulcer tabes or epilepsy have gone out of fashion but the prolonged use of silver nitrate mild silver protein or colloidal silver in nose drops¹⁰³⁵ oral sprays or paints and in genitourinary douches or instillations have produced a great number of cases of generalized argyria Some cases were observed after injections of silver arsphenamines now obsolete¹⁰³⁶ Gaul and Staud¹⁰³⁷ state that after the injection of a total of 1 Gm of silver arsphenamine argyria becomes clinically apparent

The first darkening of the skin may appear as early as six months or as late as fifteen years after the initial use of the silver drug but two to three years have been found as the average in 68 cases of the Mayo Clinic¹⁰³⁸

It is remarkable that women outnumbered the males 74 in this series

Argyria appears as a slate to bluish gray sometimes bronzed¹⁰³⁹ rarely black diffuse discoloration predominantly of the skin exposed to light¹⁰⁴⁰ Thus the forehead face neck and the dorsal of the hands are the main sites of the trouble but in severe cases the entire body surface may be involved The conjunctivae may be stippled and the caruncles of the inner canthi the gums and the palate have often been found slate colored

¹⁰³¹Lo tat-Jacob and Legrain P Lupu éryth mature trait par l'or Apparition d'un lichen plan buccal Int Bull Soc franc d dermat et syph 38 756 757 1931

¹⁰³²Throne H Elsbury J and Myers C N Unusual Clinical Manifestation Followed by Intra-venous Administration of Gold Compounds Arch Dermat & Syph 25 491 507 1932

¹⁰³³Teleky L Cew blische Argyria Zbl f Gwerb hyg 2 1 5 133 1913

¹⁰³⁴Harker J M and Hunter D Argyria Brit J Dermat 47 441 1935

¹⁰³⁵Woodward M R Argyria From the Use of Colloidal Silver Iodide I transaction Am J Dis Child 45 1010-1049 1933

¹⁰³⁶Spiegel L A Discoloration of the Skin and Mucous Membranes Resembling Argyria Followed by the Use of Silver and Silver Arsphenamine Arch Dermat & Syph 23 65-66 1931

¹⁰³⁷Gaul L E and Staud A H Chemical Spectroscopy Seventy Cases of Generalized Argyria JAMA 104 134 139 1933

¹⁰³⁸Ellis W H and Montgomery H Argyria With Special Reference to Cutaneous History Arch Dermat & Syph 44 554-599 1941

¹⁰³⁹Rei haue Argyria Arch Dermat & Syph 21 706 1930

¹⁰⁴⁰Stillians A W Argyria Arch Dermat & Syph 35 67-77 1937

large flat papules which have a tendency to coalesce into large plaques of the lichen corneus type¹⁰¹

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Hyperkeratoses and diffuse *keratoderma* after gold treatment are very rare^{107 108 109}

Oral symptoms of gold eruptions have frequently been described. Dryness and metallic taste are often the first symptoms of gold intolerance. Simple erythematous or vesicular stomatitis may occur with edema and ulceration of the tongue in severe cases. Gold stomatitis has been seen to precede rashes¹¹⁰. Clinically and histologically typical oral lichen planus almost always without accompanying cutaneous lichen planus has been noticed relatively often^{111 112 113} as a sequel of gold intolerance. The lesions are white irregular thin or slightly

¹⁰¹ Cougrot J. and L. Lichen ou prurigo verruqueux int. nae et très étendu. Bull. Soc. franç. de dermat. et syph. 43: 155-195 1936

¹⁰² Czerny A., Horowitz A. and Souillard J. Iguémentation en nappes et acné cornéocutivées à un erythrodermie aurique. Bull. Soc. franç. de dermat. et syph. 40: 1616-1619 1933

¹⁰³ Jorgensen K. Keratol. ma and V. lanod. ma accompanying Th. rapy With a Gold Compound. Arch. Dermat. & Syph. 31: 64-69 1936

¹⁰⁴ Koch A. G. Chrysiasis. Arch. f. Dermat. u. Syph. 178: 3-330 1919

¹⁰⁵ Schulz O. F. I. Chrysiasis. Arch. Dermat. u. Syph. 41: 416-427 1911

¹⁰⁶ Lorenzen J. N. Ueber das Auftreten von Chrysiasis bei f. f. f. mit Natriumau. othio. sulfat. Handl. u. Lung. tuberkulösen. Klin. d. Tuberk. 75: 685-696 1931

¹⁰⁷ Roxturgh A. C. Page A. P. M. and Gordon D. Cold. D. rmatitis With Hyperkeratosis. Brit. J. Dermat. 45: 13-142 1936

¹⁰⁸ Fournier L. and Boltanski H. Gold. D. rmatitis. Rev. de stomatol. 64: 656-19-6 Zbl. 23: 6-9

¹⁰⁹ Finnerud C. W. Lupus erythematodes der Mundschleimhaut. Arch. f. Dermat. u. Syph. 149: 318-327 1935

¹¹⁰ Mohrmann H. H. L. L. E. m. planus der Mundschleimhaut nach Gold. Handlung. Dermat. Wchnschr. 99: 1373-1386 1934

of argyria but fails to do so in other metallic discolorations e.g. that caused by bismuth. This method of treatment has not yet found general acceptance mainly because it is quite painful.¹⁰⁴¹ Argyria is an almost permanent trouble. Only occasionally has spontaneous usually incomplete regression been reported.

Lead

The skin in lead poisoning is said to be allow and dry, often itchy. Erythemas, pustular eruptions and petechiae occur.¹⁰⁴² The workers who have symptoms of lead poisoning show an incidence of dermatoses mostly dermatitis which is about three times larger than among the workers in the same industry without symptoms of saturnism. The incidence is particularly high in the group with gastrointestinal disturbances. *Hematoporphyrinemia* which is common in chronic lead poisoning is a factor in the pathogenesis of these dermatoses.^{1044 1045} However actual sensitization of the skin to lead is very rare.¹⁰⁴⁶ In rare instances metallic pigmentations have been seen. The well known *gum line* is a deposit of black lead sulfide produced by the hydrogen sulfide which develops in the tartar. The line is blue, black or gray and follows the edge of the gums. The removable deposits on the border of the gums may also be discolored.

Dystrophy and even loss of the nails from lead is known. Pain in the nails may indicate nervous disturbances.¹⁰⁴⁷

Bismuth

Bismuth may although very rarely cause diffuse blue black discoloration of the entire skin which resembles argyria.¹⁰⁴⁸ Circumscribed and in some instances extensive black pigmentations of the lips,¹⁰⁴⁹ vagina,¹⁰⁵⁰ and other mucosal surfaces have been described.

These however are rare considering the large number of luetics who have been treated with bismuth without any evidence of such discolorations.

¹⁰⁴¹ Rut A. C. et al. he s hädigung durch Hg, Pb und Bi in Opp nh im Rille Ullmann'schädigungen d. H. ut durch B. ruf und g. w. rüch. Arb. it. Vol. II. Leipzig 1908. Leopold Voss pp. 161-167.

¹⁰⁴² Filizade G. H. et al. of L. al. in C. rtain H. matoses. Soviet vrach. bur. III. 557-565. 1939.

¹⁰⁴³ Ugg. h. im R. Bi. l. k. m. s. h. w. iz med. Wchnsch. III. 277-30. 1933.

¹⁰⁴⁴ F. g. th. it. W. s. l. Merckamp W. J. Bi. l. g. ftu. x. H. mat. Wchnsch. 102. 54. 00. 1936.

¹⁰⁴⁵ s. hwar. L. an. l. Tullpa. L. O. up. tional. Bi. l. es of the Skin. Philad. l. p. la. 1939. Lea & Febiger.

¹⁰⁴⁶ Luetl. H. C. Sutto. D. C. McMillan C. J. and Mu. h. l. berg. r. G. W. G. n. r. all. ed. Discoloration of Kin. Resem. H. g. Argy. ia. Follo. ing. Proj. ned. Oral. l. s. of Bi. muth. Case of Bi. muthia. Arch. i. t. Med. 57. 1115. 1936.

¹⁰⁴⁷ Ajmo. B. D. Bi. muth. i. m. s. ed. r. Tijdsch. Geneesk. pp. 74. 745. 1937. Zbl. III. 404.

¹⁰⁴⁸ Win. K. V. gin. l. M. lanosis (caused by Bi. muth. Th. rapy. an. l. Carci. oma of th. Cervix. Arch. D. rmat. & Syph. 42. 33-39. 1910.

Pruritus, nitritoid crisis,¹⁰⁵¹ urticaria morbilliform scarlatiniform pityriasis rosea like^{105 10 3} or lupus erythematosus resembling¹⁰⁵⁴ eruptions, acne,¹⁰⁵⁵ and exfoliative dermatitis^{1056-10 9} have occurred. They are rarer generally less severe and they do not have the importance of the corresponding arsenical phenomena¹⁰⁶⁰



Fig. 151.—Blue line at gingival margin from bismuth medication

The only common surface sign of bismuth poisoning is the *blue gum line* which corresponds entirely to the blue line of lead. The bismuth line can often be observed during antilutic treatment especially around bad teeth. The line disappears several months after the discontinuation of the treatment. Severe

¹⁰⁵¹Hutin E. and Beton A. C. Les nitritoides consécutives aux injections de bismuth. *Paris méd* 2 476-47 1937

¹⁰⁵²de Wolf H. F. Dermatitis Medicamentosa Bismuth. *Arch Dermat & Syph* 28 503-511 1937

¹⁰⁵³Fox H. C. Generalized skin reaction and Dermatitis following Bismuth Therapy. *Arch Dermat & Syph* 33 353-358 1937

¹⁰⁵⁴Legrand O. and Legrand A. Accidents cutanés non-sigales encore au cours de traitement bismuthique oncosulfureux (Lésions erythrodermiques à extinction centrifuge simulant le lupus érythémateux). *Rapport Congr Dermatologistes Langue Franç* 1935 pp 42-44

¹⁰⁵⁵Tissié F. Suivi d'un rare accidentellaire à l'usage du bismuth. *Arch Dermat Syph* 30 51-53 1935

¹⁰⁵⁶Houlier Gasté J. Hacouchot J. et Lion J. Intolérance au bismuth avec hyperthermie et éruption généralisée desquamante à type de polynurie. *Bull Rx franç d dermat et syph* 41 569-57 1937

¹⁰⁵⁷Maumon H. Bismuth Dermatitis. *Zbl Bakt* 71 48-50 1934

¹⁰⁵⁸Nerlas J. Roussel J. et Thomas A. Erythrodermie importante au cours d'un traitement par l'hydrosulfure de bismuth. *Bull Rx franç d dermat et syph* 41 517-518 1937

¹⁰⁵⁹Roussel J. Erythrodermie à bismuthique chez un syphilitique ayant fait une érythrodermie arsenicale. *Cas de dermat* pp 340-343 1931 71 48-49

¹⁰⁶⁰Juliaberg F. Die Nebenwirkung der Bismuthbehandlung. *Hanbl d H u Ok* 18 44 479 19 5

ulcerative¹⁰⁶¹ even fatal¹⁰⁶ stomatitis or glossitis may also develop but this is much rarer than in mercury poisoning

Mercury

It has almost been forgotten that mercury is able to produce the same types of rashes which occur due to arsenic gold bismuth and other metals. Urticaria follicular and diffuse erythema morbilliform scarlatiniform and papular rashes and also exfoliative¹⁰⁶³ dermatitis are known. However they are less common and also less dangerous than the corresponding arsenical dermatoses. Macular rashes resembling erythema infectiosum were established as mercury eruptions due to the administration of calomel and the filling of dental cavities with amalgam¹⁰⁶⁴. The rashes are often the only symptom of mercury intoxication¹⁰⁶⁵. Scaling and diffuse or reticular hyperpigmentation may follow the erythroderma¹⁰⁶⁶.

The most important surface symptom of mercurial poisoning is stomatitis. Almkvist¹⁰⁶⁸ who has devoted so much effort to the study of mercury poisoning suggested that H_2S which develops in the decomposition of proteins under the gums and in inaccessible pockets of the oral mucosa forms HgS with the mercury carried by the bloodstream. He also found that mercury sulfide is more irritant to the oral mucosa than other metal sulfides. The first deposits of HgS are found in the loops of the capillaries of the papillae.

The first clinical symptoms are usually salivation metallic taste and a feeling of excessively long or dull teeth. Soon the gums start to swell and form pockets between them and the teeth in which pus is retained permitting prolonged contact of H_2S with the circulating mercury.

The inner lining of these pockets is the first site of superficial necrosis. From there the stomatitis which is soon complicated by infection spreads to the open surfaces of the gums where pseudo membranes and ulcers quickly form if the process is not halted by treatment and discontinuation of the mercury. In severe cases the entire mouth may become affected the tongue edematous the tonsils ulcerated the teeth loose and even pneumonia and fatal sepsis have in the days of the mercurial therapy of syphilis occasionally occurred¹⁰⁶⁶.

Treatment consists of cleaning and disinfecting the pockets with thin pointed cotton applicators dipped in strong silver nitrate tincture of iodine or any other strong astringent and disinfectant. Naturally the teeth should be kept meticulously clean and another drug should be substituted for the mercury preferably the nonmetal penicillin.

¹⁰⁶¹Matras Stomatitis ulcerosa et necroticans bismutica Zbl 56 441

¹⁰⁶²Beerman H Fatalities Due to Bismuth in the Treatment of Syphilis Arch De mat & Syph 26 797 801 1937

¹⁰⁶³Almkvist J Quecksilberschädigung Handl d H u Gk 18 175 237 193

¹⁰⁶⁴May F Über Quecksilberexantheme bei Kindern S h n i z med Wch schr 60 947 945 1930

¹⁰⁶⁵Cougerot I Blum J Bral x and Ar hambaud R Pigmentation réticulée to lqu après erythroderma hydrargyrique Arch d mat-syph Hôp St Louis 4 366-3 4 193

¹⁰⁶⁶Picard M Maurel M and T m rson Stomatite mercurielle gangréneuse mortelle Bull Soc franç de dermat et syph 100 1004 1936

Aluminum

Urticaria dermatitis pruritus herpes spider nevi perniones brittleness and longitudinal lines of the nails and paronychia are the skin manifestations of a syndrome which Spira¹⁰⁶⁷ believes to be caused by chronic aluminum poisoning

Thallium

Thallium is a heavy metal which can produce all the toxic effects of this group. Sufficient doses cause severe pains in the limbs especially in the knees salivation stomatitis gastrointestinal and liver symptoms nephritis cystitis peripheral neuritis and disturbances of the central nervous vegetative and endocrine systems^{1068 1070}

Dermadromes—A peculiar affinity for the hair causes shedding of the head hair by doses which do not cause other toxic symptoms. It is still controversial whether this effect on the hair is due to local damage¹⁰⁷¹ or whether it is evidence of an elective disturbance of the endocrine sympathetic system¹⁰⁶⁹

Thallium acetate has been for its effect on the hair widely used in the treatment of tinea of children.*

If 6 to 8 mg of thallium acetate per kilogram body weight is given in one dose the hair starts to fall after one week and complete baldness of the head is reached after nineteen days¹⁰⁷

The eyebrows especially the medial portion the eyelashes the lunula the pubic and axillary hair and in experimental rats the whiskers prove more but not entirely resistant¹⁰⁷². The epilation of the scalp is occasionally spotty. After 3 to 4 weeks the hair starts to grow again and reaches its old vigor after 2 to 3 months. This amazing treatment has however been largely abandoned because of a number of fatal poisonings which have occurred either by overdosage or by administration to adult patients or though very rarely in spite of all precautions¹⁰⁶⁸. Hypohidrosis is one of the sympathetic effects of thallium. Other dermadromes of thallium poisoning are rare. They include urticarial erythematous¹⁰⁷³ macular and lichen planus like exanthems. After severe single dose poisonings which have frequently been caused by the ingestion of rodenticides containing thallium salts white transverse nail bands comparable to

*There is no use that only children up to 10 years should be treated with thallium. The per kilogram doses which are relatively harmful to children prove highly toxic in adults.

¹⁰⁶⁷Spira L. Thallium als a part of Chronic Poisoning by Aluminum and its Alloys. London 1933. John Ballison & Danielsson Ltd.

¹⁰⁶⁸Karrberg C. I. Nebenwirkungen bei thalliumacetatbehandlung von Thallium. Zbl. 42: 131 193 1933.

¹⁰⁶⁹Buschek A. and Fischer H. Die toxische Wirkung und die bakterielle Wirkung des Thalliums. Erg. in. allg. path. u. path. Anat. 25: 17 1931.

¹⁰⁷⁰Buschek A. and Fischer H. Erg. in. allg. path. u. path. Anat. 25: 17 1931.

¹⁰⁷¹Truett C. Arizona Biologica 4: 11 1289 1909 1912.

¹⁰⁷²C. L. Wasylyk. Erkrankungen der Haare und der Haarboden. Handb. d. H. u. G. 11: 11 1931.

¹⁰⁷³Truett C. Thalliumvergiftung. Zbl. 51: 621 1933.

¹⁰⁷⁴Philaliphy A. Hautschädigungen durch Thallium. Dermat. Wechschr. 98: 78 80 1931.

Mees's bands in arsenic poisoning have been described^{1876 1875} and thallium has been found in the nails¹⁸⁷⁶. The local application of salve containing thallium acetate for the purpose of epilation has proved effective but has resulted in a great number of systemic poisonings.

Carbon Monoxide

Carbon monoxide poisoning rarely causes skin manifestations. Shillito, Drinker and Shaughnessy¹⁸⁷⁷ did not mention any skin damages in their survey of 21 143 cases but it seems that this report did not pay enough attention to the cutaneous symptoms.



Fig. 155.—Localized gas gangrene following carbon monoxide poisoning. (From Shillito et al. J. M. Soc. New Jersey.)

The cherry red lips and deep cyanosis of persons poisoned with monoxide gas is generally well known. Local edema of the extremities was known to the older observers. It may be related to the circumscribed necroses found after severe gas poisonings¹⁸⁷⁸⁻¹⁸⁹⁰. The lesions start as serous or hemorrhagic bullae which

¹⁸⁷⁵Adler A. Vagtskrankung bei Thalliumvergiftung. Dtsch. Ztschr. 63: 259-261, 193.

¹⁸⁷⁶Wilkinson W. Fall von akuter Thalliumvergiftung. Zbl. 52: 193, 1935.

¹⁸⁷⁷Shillito F. H., Drinker C. and Shaughnessy T. J. The Problem of Nervous and Mental Sequelae in Carbon Monoxide Poisoning. J. A. M. A. 108: 669, 1936.

¹⁸⁷⁸Bernstein H. Hautkrose bei Kohlenoxydvergiftung. Zbl. 46: 6, 1933.

¹⁸⁷⁹Oppenheimer G. Umschriebene Hautgangrän und Purpura nach Leuchtgasvergiftung. Zbl. 42: 161, 193.

¹⁸⁹⁰Shillito F. A. Factors in Peripheral Skin Lesions Following Carbon Monoxide Poisoning. J. M. Soc. New Jersey 40: 415-4, 1913.

develop into deep sharply outlined round ulcers or patches of dry gangrene. Such necroses have been seen on the heels, soles, ankles, malleoli, sacral area, fingers and scalp. In several cases an entire limb was affected.^{1091, 1092}

Perhaps decubitus is at least in some cases a factor in the pathogenesis of the ulcers but there are clinical and histological reasons to blame primary vascular damage instead.

Herpes zoster especially of the forehead is considered to be a characteristic sequel of monoxide poisoning¹⁰⁹³ (Schas in discussion to Fischer¹⁰⁸⁶).

Sedatives

The *barbiturates* quite frequently produce rashes of allergic character. Pruritus and urticarial macular, scarlatiniform, multiform or petechial exanthems are fairly common and well known especially from phenobarbital. Bullous eruptions in the mouth have also been observed.¹⁰⁹⁴ The severe and in some instances fatal cases of exfoliative dermatitis are fortunately very rare.¹⁰⁹⁵

Nirvanol is a hypnotic which almost constantly produces a morbilliform exanthem after 6 to 14 days of regular administration. The rash is accompanied by conjunctivitis, stomatitis and other mucosal reactions, fever, cyanosis, dizziness and other nervous symptoms, gastrointestinal and hepatic symptoms and albuminuria, a syndrome which is known as *nirvanol disease* (V. Pfaundler after R. L. Mayer¹⁰⁹⁶). Nirvanol is used in the treatment of chorea. The therapeutic result depends on the development of the nirvanol allergy.¹⁰⁹⁷

Bromine

Morbilliform, urticarial, bullous, vesicular, vacciniform and other rashes are occasionally seen after the administration of bromide. More characteristic are acneiform eruptions which appear at the predilection sites of acne vulgaris especially on and around the nose. It seems that bromine acne is more apt to suppurate and to form flaccid pustules than the common juvenile form.¹⁰⁹⁸

In some cases ulcers form which by central healing and partial peripheral advance may resemble tertiary syphilis. A peculiar feature of some bromine reactions is the tendency to develop tubercous or tumor like vegetations. The bromoderms are known in several varieties and combinations. They occur as papillomatous, confluent, crustous, suppurative or ulcerating, sessile or tubercous, usually painful eruptions. Small subepidermal abscesses in the edges of the lesions may create a blistomycosis like picture. After the expression of pus from large lesions a quite characteristic cribriform surface results.¹⁰⁹⁹

¹⁰⁹¹Fuhrer N. and Spillberg G. Längere von Lower Extremität Füllung Carbon Monoxid. *Archiv für Klin. Path.* 11: 111-116 1916.

¹⁰⁹²Drinker C. H. Carbon Monoxide Anaphylaxis. New York 1929. D. Ford University Press.

¹⁰⁹³Knappe A. H. Eine Falle von Herpes Zoster. *München med. Wochenschr.* 87: 346-39 1910.

¹⁰⁹⁴Fischer V. Falle von Hautveränderungen bei Leuchtgasvergiftung. *Zbl. f. Bakt.* 10: 107-109.

¹⁰⁹⁵Hoffmann M. Pharyngeal Friction of the Mouth Arch. Dermat. & Syph. 25: 663 1922.

¹⁰⁹⁶Junstowicz A. Leber Dystrophie—Allergie. *Med. Woch.* 29: 189-191 1923.

¹⁰⁹⁷Mayer R. L. Nirvanol Frictions. *Arch. Dermat. & Syph.* 28: 1065 1923 1927.

¹⁰⁹⁸Kleinberg L. Toxicodermis. *Hautb. d. H. u. Gk.* 2: 23-375 1923.

¹⁰⁹⁹Netherton E. W. Nodular Papillomatous Bromoderma. *Clinical Clin. Quart.* 11: 10-24.

The bromodermas are most often seen on the lower legs and vary widely in size and number of lesions. There may be a few or several hundred and some may be as small as peas while others may reach the size of a fist¹⁰⁸⁸. The various types of lesions may be seen in the same patient at the same time. A characteristic foul odor may be present¹⁰⁸⁹.

The lesions have occasionally been first observed several months after the ingestion of bromine had been discontinued. Bromoderma sometimes develops out of other pre existing skin lesions ■■ ulcers scars and injuries. The tongue and other parts of the mouth may participate in the fungating process.

The allergic character of the bromodermas has been recognized by most authorities but is disputed by some investigators¹⁰⁹⁰ mainly because of negative skin tests.



Fig. 138 —Acneiform eruption from bromine

The passive transfer of the allergy to the guinea pig has occasionally been demonstrated¹⁰⁹¹. Bloch and Tenchio¹⁰⁹ elicited in their case of severe bromoderma with fatal outcome positive patch tests after 24 hours. Later these reactions turned into bromoderma an interesting demonstration of Koebner's phenomenon¹⁰⁹². Positive scratch and intradermal tests have also been elicited¹⁰⁹⁴. Excessive eosinophilia is another argument in favor of the allergic nature of the bromodermas. The vegetations have several times been found to be free of bromine. The diagnosis of the bromine dermatoses has to consider such heterogeneous diseases as the acute exanthems, acne vulgaris, syphilis, blastomycosis, epithelioma, mycosis fungoides, erythema nodosum and others.

¹⁰⁸⁸Lehner E. Bromoderm. Zbl. 53. 79. 1936.

¹⁰⁸⁹Soroka F. I. Bromoderma Vegetans. V. nerol. i. de mat. 8. 52-56. 1931.

¹⁰⁹⁰Bloch B. & d. Tenchio M. Bromoderma Vegetans. Arch. f. Derm. u. Syph. 185. 93. 148. 193.

¹⁰⁹¹Haeumann H. Bromoderma und Hautallerg. Arch. f. Kinderh. 210. 103-107. 1937.

¹⁰⁹²B. nhardt H. Acne bromata provocata. Arch. f. Dermat. u. Syph. 171. 11. 114. 1934.



Fig 157 —*Bromodroma tuberosa* (From Netherton E W Cleveland Clin Quart)



Fig 158 —*Bromodroma tuberosa* (From Netherton E W Cleveland Clin Quart)

The copper or brownish hue of the bromodermas is often emphasized

Discontinuation of the bromides and large amounts of fluid and sodium chloride¹⁰⁹⁵ are important in the treatment

The prognosis of treated cases is generally favorable if the use of bromides is discontinued Scarring and pigmentation are common sequelae Rarely the lesions continue to develop despite discontinuation of the drug and treatment Such cases may end fatally¹⁰⁹

Iodine

The eruptions following the internal use of iodine and its compounds follow the pattern of those produced by bromine Acne is the most common dermatome of iodism Vesicular bullous¹⁰⁹⁶ and hemorrhagic eruptions have been seen more often than the vegetating forms The allergic nature of the iododermas and the sensitizing effect of iodized table salt¹⁰⁹⁷ has been established by experimental investigations¹⁰⁹⁸

Fatal cases of iododerma tuberosum are very rare^{1099 1100}

Some Other Drug Eruptions

Almost all drugs and poisons are able to produce allergic skin eruptions Among the great number of multiform morbilliform scarlatiniform eczematoid hemorrhagic bullous vesicular and other exanthems a few stand out because of unusual clinical features

Phenolphthalein eruptions are well defined round or oblong red and later purplish brown spots They sometimes appear as large bullae The macular lesions are lentil to palm sized and are most often seen about the buttocks and the lower back but also on the extremities

The bullae are large and deciduous leaving an erythematous and pigmented base Eczematous forms are less well known The lesions may after an inflammatory stage recede and leave only a faint pigmentation It is a peculiarity of the phenolphthalein eruptions to appear in exactly the same sites even after complete or almost complete disappearance and after long intervals This is known as the *fixed eruption*

¹⁰⁹⁵Wig J J Purth & Contributions to the Experimental Aspects of Iodid and Bromid E
anth m Arch Derm & Syph 8 407-410 1913

¹⁰⁹⁶Spillm W L and Malton E milte bulles généralisés de l'origine iodique chez une h mi
plégique Bull Soc fra de dermat et syph 40 1754 1756 1933

¹⁰⁹⁷Reich I F Iodized Table Salt as an Etiologic Factor in Iododerma Arch Dermat & Syph
89-536 1934

¹⁰⁹⁸Isaacs C Eline It n Iom v Jode anth m Jap J Dermat 33 130-131 1932 Zbl 33

¹⁰⁹⁹Hand I and Fittma G H Fatal Iododerma Arch Dermat & Syph 24 9-241
1936

¹¹⁰⁰Henzeberg H and Maschke Jenson L Ueber Thromboangiitis obliterans (Bisfang z
Pthog nes des Iodod ma bulbosum veg ta m) Beitr z path Anat u z allg Path 94 353-360 1934

¹¹⁰¹Ell J J and F x F C Fatal Iododerma Arch Dermat & Syph 24 745-757 1931

Phenolphthalein is an ingredient of more than a hundred proprietary laxatives¹¹⁰. Similar fixed eruptions also occur as a reaction to *antipyrin*¹¹⁰³. The eruption to either drug may develop within an hour after ingestion. Severe melanoderma after phenolphthalein is very rare¹¹⁰⁴.

Sedormid a mild sedative of the urea group has in many cases caused severe thrombocytopenic purpura^{110 1107}.

Veramon a popular European combination of barbitol and amidopyrin may give rise to fixed symmetrical eczematous patches and mucosal swellings. Its use has been discouraged because of the danger of *agranulocytosis* from the amidopyrin content.

Quinine eruptions are most often scarlatiniform. In severe cases exfoliative dermatitis may develop. Severe purpura is a rare event. About one out of 200 patients is or becomes allergic to quinine¹¹⁰⁸.

Atabrine which proved to be a satisfactory substitute for quinine may cause a lemon to sickly greenish yellow discoloration¹¹⁰⁹ after one to four months of use. The yellow dyschromia is uneven in contrast to icterus with the heaviest discoloration on the exposed parts and in the folds of the body. The sclerae remain white. The extensor¹¹⁰⁹ surfaces of the arms and feet the webs the nape the forehead and the circumoral area are most deeply stained. A golden ring around the mouth is a peculiarity of the atabrine pigmentation. Unlike the discoloration in carotinemia the palms are less yellow than the dorsa of the hands.

Bluish pigmentations have been seen in the hard palate epiglottis tracheal rings and the nail beds.

During the war in the South Pacific especially in New Guinea many cases of a dermatosis with features both of an *atypical lichen planus* and *eczematoid dermatitis* occurred among the troops who took atabrine regularly for the suppression of malarial but it is not generally recognized that atabrine is the cause¹¹¹⁰. The condition is characterized by various combinations¹¹¹¹ of purplish hypertrophic lichenoid papules and plaques frequently with a rough verrucous surface and eczematoid plaques in all stages of erythema oozing and scaling.

¹¹⁰⁰Belote G H and Whitney H A K. Phenolphthalein Compounds Arch Dermat & Syph 26 279-281 1937

¹¹⁰¹Basch G and Sainton J. Plaque érythémato-pigmentée fixe et étiém nts bull ur & type é y thème polymorphe par ingestion de ca blets à base d'antipyrine Bull Soc franç de dermat et syph 42 453-455 1935

¹¹⁰²Wells H S. Dermatitis Medicamentosa (I phenolphthalein) Arch Dermat & Syph 23 118 1931

¹¹⁰³Falconer E N and Schumacher J C. Purpura Hemorrhagica Due to Ingestion of Sedormid (Allyl isopropyl acetyl-carbamide) Arch Int Med 63 1 137 1940

¹¹⁰⁴Loewy F E. Thrombop ic Hemorrhagic Purpura Due to Sedormid Allergic Effect Lancet 1934 I 845-846

¹¹⁰⁵Huber H. Case of Purpura Hemorrhagica Resulting From Sedormid J A M A 113 674 675 1939

¹¹⁰⁶Haue A. Leber Chlinitis und Chl indiosynkra I. Monatsschr med Wchnschr 61 332-336 1935

¹¹⁰⁷Schechter A J and Taylor H M. Atabrine Pigmentation J A M A 92 640-650 1936

¹¹⁰⁸Espstein F. Lichen Planus-Eczematoid Dermatitis Compl of Southwest Pacific Bull U S Army M D pt 5 89-897 1945

¹¹⁰⁹Untoward Reactions Attributed to Atabrine (Atypical Lichen Planus) J A M A 129 1091 1093 1945

The dermatosis may also though rarely consist of lichenoid elements alone. More frequently the eczematoid lesions dominate the picture entirely even to the extent of severe generalized *exfoliative dermatitis*.

The legs and forearms the dorsal surfaces of the hands and feet and the face neck buttocks and genitalia are predominantly and symmetrically affected. Atrophy and hyperpigmentation nail changes and shedding of the nails patchy alopecia and dyshidrosis have been described as late sequelae.

With the exception of severe exfoliative dermatitis the course is generally benign if itabrine is discontinued.

Picric acid may cause generalized *yellow discolorations* which simulate icterus. The sclerae take part in the staining.

The *sulfonamides* may cause a great variety of eruptions which are essentially the same as those due to the barbiturates the arspenamines and many other drugs. A special feature is the frequent *photo sensitization* caused by the use of sulfonamides.

Ephedrine besides occasionally causing generalized erythemas and dermatitis has in some persons a tendency to produce urticaria and local swellings especially of the eyelids.^{111 114}

Codeine rashes¹¹⁵ have been described as follicular erythemas which quickly develop into scarlatina like exanthems. Codeine and opium occasionally produce pruritus or formication.¹¹⁶ Paresthesias are also a dominant symptom in chronic *ergotism* from¹¹⁷ *Claviceps purpurea* infected rye and wheat and in ustilaginism from corn infected with *Ustilago maydis*.¹¹⁸ Even acrodynia like cases of morbus cerealis have become known. In *favism* a severe poisoning occasionally caused by the eating of broad beans (*vicia faba*) purpura is an important symptom.¹¹⁹

Dinitrophenol the dangerous weight reduction agent caused urticarial macular maculo papular and eczematoid rashes in 7 to 20 per cent of the treated persons.^{110 111} The frequent *yellow discoloration* is due to the staining and is not caused by icterus.^{112 113}

¹¹¹Julien R and Loran J. M. Dermatitis Medicamentosa Due to Ephedrine. J Allergy 3 48-49 1934

¹¹²Ayres J. R. and Anderson J. P. Dermatitis Medicamentosa Due to Ephedrine. JAMA 97 437-440 44-45 1931

¹¹³Thurman W. F. W. and Noun M. H. Ephedrine Dermatoses. JAMA 45 27-28 1933

¹¹⁴Schroer M. and Kell H. The Skin Eruptions of Codeine. JAMA 102 909-910 1934

¹¹⁵Goldsmith W. N. Significance and Treatment of Itching. Practitioner 142 36-54 1939

¹¹⁶Kauitz J. Chron. Entom. Egoth. It. H. lat. n. to the Vasomotor and Trophic Dis. Arch. Int. Med. 47 548-64 1931

¹¹⁷Mayhoffer H. Lettack. Eius. elio. bl. r. un. b. n. te. Form. alim. (Er. r. q. t. ung. bei. ler. Mal. ern. hrung. im. kind. alter. Med. F. egl. 8 153-157 1931. 211 29 - 11

¹¹⁸Jimenez Diaz C. and Biol C. M. Anaphylact. Purpura Due to Sensitization to Beans (Purpura Form of Favism). F. v. clin. espan. 8 1-9 130 194

¹¹⁹Frumess O. M. Allergic Reaction to Dinitrophenol (Case). JAMA 102 1-10 19 1934

¹¹⁰Kesten H. M. Dermatitis Medicamentosa Formula 91 (Dinitrophenol). Arch. Dermat. A Syph. 21 73-75 1934

¹¹¹Smolin M. Dinitrophenol and Dehydrated Thyroid in Treatment of Obesity. JAMA 108 110-117 193 193 193

CHAPTER XIV

DISORDERS OF THE CIRCULATION

Heart Disease

Cardiac decompensation no matter what its cause may be produces a rather uniform syndrome with dyspnea cough palpitation and precordial distress dominating the complaints. Cyanosis and edema are almost always present.

Cardiac Decompensation—*Cyanosis* is not only caused by the deficient blood circulation. If the state of decompensation lasts for some time the respiratory system suffers and the oxygenation of the venous blood becomes insufficient increasing the cyanosis. Cyanosis is an early sign of valvular heart disease especially of the right heart but also though later of the mitral valves. It is less pronounced in aortic insufficiency.¹¹

Extreme degrees of cyanosis are encountered in the *newborn* infant with *congenital affections of the heart*. In contrast to the cyanosis in acquired and adult types of heart disease the blue discoloration may cover the entire body surface of the baby (*Morbus caeruleus*). In later life the cyanosis is usually restricted to or at least most marked in the *acra*. The cheeks the lips the nose the ear lobes the finger tips the toes the elbows and the patellae are chiefly affected.¹² Frequently only a slightly purplish hue of a seemingly healthy complexion indicates an underlying cardiac insufficiency. The cyanotic parts especially the feet and lower legs are cool.

If cyanosis exists for a longer period sharply drawn *telangiectases* appear. On the face they resemble *rosacea* or they are the first stage of *rosacea*. *Telangiectases* occur also on other parts of chronically congested skin e.g. between the shoulder blades and on the abdomen.¹³

Edema usually is seen first in the skin about the ankles but later it may involve the entire skin and the subcutaneous tissues. Chronic congestion may cause *clubbing* of the fingers and toes more so in children than in adults.¹⁴

The skin in chronic congestion is if not yet cyanotic *pale* and often grayish. Slight *hemorrhagic* tendencies are an early sign of decompensation though they may be only detected by the tourniquet test or the capillary cope.¹⁵ Nagel mentions extravasations over the thorax and epigastrium in decompensated mitral insufficiency.

The *pallor* of the patients with mitral stenosis before the cyanosis occurs is marked.¹⁶

Hyperpigmentation occurs—especially in children—on the forearms and the dorsa of the hands and fingers. The pigment is *hemosiderin* from the extravasa-

¹¹Seckl H. Chronisch Stauung haut beim Kind. Monatsschr f Kinderh 45: 394-403 1909

¹²Jürgensen F. Okkulte Hautstörungen. Deutsches Arch f Klin Med 176: 9-4 1931

tion ^{1123 1124} Slight *jaundice* is frequent. It appears less pronounced in the edematous parts ¹¹²⁵. Increased *freckles* are often seen in juveniles with decompensated mitral insufficiency ¹¹²⁶.



Fig. 150 —Dermatitis of leg exacerbating and receding with cardiac decompensation



Fig. 160 —Dermatitis of the leg in hypertensive necrosis of the heel with the degree of cardiac decompensation

Hypertrichosis is a symptom of chronic congestion in children. The back, the face and the extensor aspects of the extremities exhibit the increased lanugo most distinctly.¹¹³

Eczema of the lower legs sometimes with a purpuric component is an occasional accompaniment of decompensation. The healing with improvement of the circulation and relapse on recurrence of decompensation is proof of the circulatory factor in these eczemas.



Fig. 161.—Schamberg's dermatosis in circulatory stasis. (Courtesy Dr. M. Jeanneret.)

The *pulsating erythema* of the nail bed or of a dermatographic line known as the capillary pulse is a well known sign encountered in aortic insufficiency but also in other conditions. The jerking pulsation can be demonstrated in the capillarscope.¹¹⁴

Arteriosclerosis, Hypertension

Arteriosclerosis affects the arteries of the skin¹¹⁵ as well as those of other organs (see Chapter on Old Age). The capillaries appear tortuous and thin in the capillarscope (E. Weiss after H. Niekau¹¹⁶).

The clinical skin changes produced by arteriosclerosis are best observed in the feet.¹¹⁷ The skin is dry due to the impairment of the glandular functions. The nails become atrophic and brittle or thick. Corns and calluses become thicker. The lanugo hair on the dorsa of the phalanges disappears. The foot including the sole may become cyanotic on dependence and pale on elevation.

¹¹³Niekau H. Kapillari-otachtung an der Hyperostose bei Misch- und Fröhlich'scher Krankheit. Med. u. klin. Wch. 22: 479-551, 1927.

¹¹⁷Weiss E. Beiträge zur Pathologie der Gefäße kranker und gesunder Haut. III. Mitt. Di. Arteriosklerose der Haut. Dermat. Wch. 102: 697, 1926.

¹¹⁵Niekau H. Cutaneous Manifestations of the Circulatory Disorders of the Feet. J. A. M. A. 124: 747-750, 1914.

Nomland¹¹³ believes that the more nearly horizontal the leg is when pink color returns the greater is the insufficiency of the arterial supply. Wounds and infections even trivial ones heal slowly and may cause severe complications. This is the more important since *pruritus* is a common symptom of cutaneous arteriosclerosis and decompensation.¹¹²⁹

Cardiac infarction may leave its mark in cross furrows of the *nails* (Beau's lines) or more rarely in transversal white lines.¹¹³⁰ Cross furrows have also been observed on the toenails in intermittent claudication.¹¹³¹ Occasionally an *erythema* of the face and neck resembling *erythema pudoris* has been seen in *angina pectoris*¹¹³ and *hypertension*.¹¹³³

Herpes Zoster intercostalis has often been related to *angina pectoris*.¹¹³⁴

The most important though by no means constant cutaneous manifestation of hypertension is *pruritus*. It is often severe and reflects in its intensity the ups and downs of the blood pressure. Severe attacks of *pruritus* may precede apoplectic episodes. Rarer than *pruritus* alone are *eczematous* or *pruriginous* changes. It is in such cases hard to decide whether the dermatosis is due to hypertension, nephrosis or decompensation since it may accompany all of the conditions. The *eczema* sometimes seems secondary to *prurigo*, the itching papulourticarial lesions of which are quickly destroyed by scratching. A slight scab covered spot of lentil to fingernail size ensues. Groups of such lesions in various stages of development and lichenification are usually found along the legs and in some severe cases over the entire body. These cases are at least temporarily benefited by superficial X-ray therapy.

In obstinate cases of *eczema* of the hands, of nummular *eczema* and of scaling and itching of the finger tips one should consider the state of the circulation and treat accordingly.

Hypertension, aortitis, arrhythmia, chronic glomerulo-nephritis and other vascular and hepato-splenic disorders may be accompanied by pigmented and depigmented hemorrhagic inflammatory plaques on the lower legs. Favre⁹⁰ and his collaborators have stressed the internal relationship of this condition which he called *angiodermatitis pigmentosa purpurica*. He stressed that this common syndrome has nothing to do with varicose veins and that it does not show the features of *eczema*. The underlying periosteum is often early affected. The patches run a gamut of colors from yellow to blue-black. The surroundings are often depigmented. The lesions are also variable in size and contour. Hemorrhagic infiltration with formation of a black scab and ulceration occurs.

¹¹²⁹Coh N. Pruritus — dysnoisches Symptom mit Blutungsknebelung als Summation. Arch f Dermat u Syph 133 3 19

¹¹³⁰Ulrich F. White Cross Striae of the Finger Nails Followed by Cardiac Infarction. Arch Dermat 52 106 107 1945

¹¹³¹Schlesinger H. Das Nägel-symptom bei intermittierender Hinken. Med Klin 26 921 922 1930

¹¹³²Portocarrini A. and Pirra G. T. Angine de poitrine défective avec érythème initial et pouls hypertensif. Bull. t. m. n. d. Soc. med. Hép. 1 Paris 47 16 0-1654 1931

¹¹³³Weber F. P. Daily Blotchy Flushing Over Neck and Upper Thorax in an Elderly Woman With High Blood Pressure. Proc. Roy. Soc. Med 28 31 1935

¹¹³⁴Leib J. Herpes zoster bilateraler Organerkrankung. Deutsche. med. Wochenschr 52 906-908 1926

Tenderness and scaling are other features. The pigment is hemosiderin. In spite of some similarities the common angiodermatitis is to be separated from Shamberg's disease and from purpura Majocchi. Syphilis is the most common etiologic factor.

The compression of the superior vena cava by an aneurysm of the ascending aorta may cause congestion and tortuosity of the veins of the neck and face even of almost the entire upper half of the body. There is also edema and cyanosis. Pressure on one of the innominate veins produces these signs on one side only, usually the left.¹¹ A leaking aneurysm of the abdominal aorta may cause huge suggillations of the scrotum and lumbar area.



Fig. 162.—Female, age 17 years. Arteriovenous aneurysm following fracture of radius. There is a growth of the affected hand; large, nodular, angiomatous rolled vessels; increased skin temperature, hyperhidrosis and bruits. (Courtesy of Dr. Earl Schlaepfer.)

Peripheral arteriovenous aneurysms are usually caused by trauma. They cause hemangioma-like accumulations of tortuous blood vessels with pulsation and murmurs. The skin over such a lesion is warmer than normal and perspires more readily. The increased blood supply causes increased growth of the involved part including the bones.

Thrombo-Angitis Obliterans (Buerger's Disease)

In this disorder of unknown but¹¹⁸ probably bacterial etiology¹¹⁷ the peripheral arteries and veins of the legs—rarely of the arms—sometimes together with adjacent nerves¹¹⁹ are affected. Arteritis with thrombus formation in single or

¹¹⁷Buerger, E. Thrombo-angiitis obliterans of the extremities. Phila. and London, 1914. W. B. Saunders Co.

¹¹⁸Allen, F. A. Thrombo-angiitis obliterans. Bull. N. Y. Acad. Med. 18: 16, 189, 1917.

¹¹⁹Klaer, G. Thrombo-angiitis obliterans (Buerger's). Acta orthop. Scandinav. 2: 103, 13, 1931. Zbl. 28: 50, 1931, 193.

multiple foci causes a state of ischemia with severe pain. The pain may occur on exertion and then it has the character of intermittent claudication or it may be experienced while the patient is at rest. In this case the pain is continuous worse at night and sometimes aggravated¹¹³⁷ and sometimes eased by dependency. Gangrene with severe pain may occur. The course of the disease is most often chronic and slowly progressive in attacks. The peripheral pulses in the affected limb are absent or diminished. The sufferers are almost exclusively young men (98 per cent) often Hebrews (28 per cent) and heavy cigarette smokers (93 per cent)¹¹³⁹. Familial incidence has been observed¹¹⁴⁰.

Dermadromes—The skin¹⁴¹ of the toes is at least in the fairly advanced stages moist cool often scaly tender and reddish blue in patches especially if the patient stands. Elevation blanches the limb. Reactive hyperemia is apt to follow on lowering the leg except in severe cases¹¹³⁸. If the time required for the return of color while in the dependent position is longer than 10 seconds impaired arterial circulation exists. In marked impairment of the arterial circulation by thromboangitis the return often takes more than forty five seconds¹¹³⁷. Refilling of veins after emptying by elevation also takes longer than ten seconds. Superficial palpable phlebitis is a feature in Buerger's disease which leaves hemosiderin pigmentation for a long time after healing.

Variable degrees of pallor or cyanosis may follow exposure to cold or emotion¹¹³⁷. If gangrene develops it is less extensive than in arteriosclerosis because of the smaller caliber of the thrombosed arteries. It is usually of the moist type. The endangered toes are bluish especially the nailbeds. The skin is often glossy and atrophic. Subungual keritosis develops frequently. Ulceration of the big toe is the commonest form of necrosis. Gangrene of the fingers is much rarer than gangrene of the toes since the establishment of collateral circulation has a better chance in the arms than in the legs. Besides the occlusion by thrombosis vasospasm plays a part. The diagnosis has to exclude arteriosclerosis. Here the picture is very similar but the patients are older the pain at rest is milder gangrene is more apt to be dry and phlebitis and edema are not features. Lipemia is frequent in arteriosclerosis and the arteriosclerotic artery may be detected by X ray¹¹³⁷.

The treatment requires complete abandoning of smoking vascular exercise by systematic raising and lowering of the legs and warm baths. Mechanical pulsating devices do not seem to be very effective in Buerger's disease. Amputation nerve section or sympathectomy are often necessary^{1137 1141}.

Shock

Shock is characterized by circulatory failure and deep depression of the nervous functions. It may be caused by trauma hemorrhage massive infection burns intestinal perforation cardiac failure and other conditions.

¹¹³⁷Horton B F. Thrombo-angitis Obliterans 919 Cases Incidence of Amputation Mill Surgeon 84 599-600 1939

¹¹³⁸Nikolajew H. Arterielle obliterat. (Thromboangitis Buergeri) als familiäre Erkrankung Deutsche Arch. f. klin. Med. 271 391-394 1931

¹¹⁴⁰Homan H. Circulatory Diseases of the Extremities New York 1933 The Macmillan Company

In shock the effective circulating blood volume i.e. cardiac output and venous return is reduced and the peripheral flow of blood is slowed down¹¹⁴. The blood pressure is at first maintained by vasoconstrictory mechanisms but drops as soon as these mechanisms become weak. While in the initial or premonitory stage of shock the pulse may not be altered it becomes rapid and thin in the fully developed syndrome.

Dermadromes —Di Palma¹¹⁵ stresses the diagnostic importance of the skin phenomena in the initial phase the knowledge of which may enable the physician to apply help before the onset of deep shock. For the examination the patient has to be stripped and remain exposed to room temperature for at least 10 minutes. If the skin can be blanched by pressing the forefinger forcibly into it some blood must be in the skin. The color contrast with the unblanched skin and the rate of fill in of the blanched areas permit quick though rough and unreliable estimate of the peripheral blood flow. Gentle touching with the back of the digits permits the determination of gross differences between the skin temperature of the trunk and the extremities. Such differences would indicate a slow blood circulation in the periphery. The color of the skin is an excellent guide in the estimation of the rate of the peripheral blood flow. It should be judged by the hue of the cheeks the lips and especially of the nail beds. Di Palma¹¹⁶ advises the acquisition of competence by observing the nail beds under controlled conditions of circulation produced by a blood pressure cuff and varying elevation of the arm. Brick red purplish and finally deep purplish blue indicate the degrees of peripheral circulatory failure.

Since the brick red hue is an early sign it is most important. Simultaneous forcible stroking of the skin with a blunt instrument on the chest and on the forearms provides an opportunity to compare the differences between the time of appearance and the color of the red dermographism. The peripheral blood flow must be considered slow if the red line appears later than five seconds and if the reaction on the forearm is delayed in comparison with the chest. The color should be bright red. Di Palma, Muss and Foster¹¹⁷ have devised a method which measures the minimal time required to elicit hyperemia by a weighted rubber ring placed on the skin of the chest and arm (stimulus time) and the time after which the hyperemia fades (clearance time). These times are compared with those obtained from a normal person in the same room.

¹¹⁴ Di Palma J R : The Circulation in the Shock Syndrome. J A M A 123 691-693 1943

¹¹⁵ Di Palma J R, Muss I and Foster E I : Relative Hyperemia Ring Test in the Study of Ischemic Lesions Caused by Aortic Atherosclerosis and Aortic Embolism. Am Heart J 31 361-191

CHAPTER XV

DISEASES OF THE KIDNEYS

The relation of dermatoses to renal disorders fascinated the physicians of the nineteenth century more than the recent generations. Bright in 1827 was convinced of the sympathy between the skin and the kidney and many famous authors have investigated this relationship more closely.³⁶

The kidneys being concerned with the excretion of water soluble substances are functionally linked to the skin. Under normal conditions the skin stores about 28 per cent of the body's water. It takes up much more in edema¹¹⁴ which is the dominant symptom in acute diffuse glomerulonephritis and in some stages of other renal diseases. The loose texture of the skin and of the subcutaneous tissue affords more storage space than the muscles or even the serous cavities are able to provide. Along with water the skin stores chlorine and minerals. The vast vascular capacity of the skin provides an important regulating mechanism of the blood pressure which is the main power behind the urinary excretion. The skin has an excretory function which however can only partially and occasionally replace renal excretion.¹¹⁵

Under normal conditions the skin as well as the kidneys excrete about 1300 cc of water daily but the kidneys are able to concentrate from the blood more than thirty times more urea and three times more NaCl than the tubules of the sweat glands. Thus even a damaged kidney usually excretes better than the skin and the skin alone is not able to replace the function of the kidneys.

Dermadromes were seen in approximately one fifth of the series of 1100 patients with all forms of nephritis and nephrosis studied by Chargin and Keil.³⁷ These authors found that skin diseases occur more frequently in association with *azotemia* than in those without azotemia. In contrast to earlier observers¹¹⁶ they found that *purpura* is the most frequent lesion associated with nephritis. All types of hemorrhagic lesions ranging from pinpoint petechiae to large extravasations were encountered. Chronic glomerular nephritis without edema seemed to predispose to hemorrhage far more than the other clinical types of *nonsurgical kidney disease*. Higher degrees of *azotemia* often cause intense purpura. Sometimes the hemorrhagic tendency expresses itself only in a hemorrhagic component of a usually nonhemorrhagic dermatoses e.g. *tinea*. *Pruritus* varying widely in intensity and in its sequelae may be the first symptom of nephritis (Oenlatory after Pringle¹¹⁶). It occurred in 20 per cent of the cases of essential hypertension with azotemia and in 12 per cent of the instances of

³⁶Kroetz C. Die klinischen Zusammenhänge zwischen Haut und Nierkrankungen. Zbl. 39 107.

¹¹⁴Fürst R. I. Schallzucker V. handb. d. Gesellsch. f. V. d. d. g. u. Stoffwechselkr. 12 21.

2 1037

¹¹⁶Pringle J. J. Skin Eruptions. In Bright. Disease Practitioner 117 540 1901

chronic glomerular nephritis with edema. Its infrequency in all other groups of the series of Chargin and Keil¹¹⁶ is striking. Azotemia is probably the inciting factor. Azotemia without pruritus occurs but if pruritus is present in uremia it is regarded as of serious prognostic importance¹¹⁷. The pruritus may be explained by *dermatitic changes* which Rossle observed in almost all of 25 cases of



Fig. 163 - Purpura. Chronic nephritis

uremia even when no gross changes were present¹¹⁷. These inflammatory changes ranged from simple perivascular infiltration to necrotic and herpetiform pandermatitis. The findings could not be confirmed entirely in an American series¹¹⁸. Here atrophy of the skin was the dominant pathologic feature. Other pathologists have cautioned not to overrate the perivascular infiltration in the skin¹¹⁹ which is often seen in glomerulonephritis.

The urea content of the skin is usually high. The appearance of crystalline urea as a thin white saltlike deposit on the skin (especially about the nose) the

¹¹⁶Rösel, H. Urmisch. *Dermatit.* Virchow Arch. f. path. Anat. 271: 301-316 1909

¹¹⁷Rosenthal, S. H. Urmisch. *Dermatit.* Arch. Dermat. & Syph. 23: 971 1931

¹¹⁸Herrlich, H. G. and Rosenthal, W. Hautveränderungen bei Nephritis. Münch. n. med. Wchnschr.

neck and the shoulders¹¹⁴⁸ is known as *urea* (uremic) *frost*. It occurs most frequently in malignant sclerosis and essential hypertension (10 to 20 per cent after Chargin and Keil²⁴). A prolonged agonial period which allows the formation of the crystals together with a high urea content of the blood and of the skin seem to be the factors accounting for its relative frequency in the mentioned conditions²⁴. The phenomenon of urea frost is more often seen post mortem than in life. It is still controversial whether the source of the urea frost is the sweat glands or the sebaceous glands. Its accumulation in the areas of accumulated sebaceous glands and its absence on the palms and soles seems to support the sebaceous gland theory while observations of crystals at the mouth of the sweat glands seem to prove the sweat gland origin. Urea frost is of ominous prognostic significance.

Erythematous bullous and urticarial eruptions in nephritis^{49 1150} have occasionally been described. Generalized exfoliative dermatitis is also mentioned in connection with the renal disease¹¹¹. Some of the dermatoses may have been caused by septicemia. Ehrmann¹¹⁵ saw in edematous patients aggregated vesicles about the head which rapidly formed oozing pink surfaces.

Fissural eczema is supposed to be more common in nephritis without edema. Grouped papular eruptions of great obstinacy were in the older literature known as *erythema papulatum uremicum*⁴⁹ (Merk after Ehrmann¹¹⁵).

It may be mentioned in this connection that rabbits with experimental glomerular nephritis could be shown to be more sensitive to skin irritation from tar than the normal controls¹¹⁵³.

A progressive febrile dermatosis probably of bacterial origin occurring relatively often in *lipid nephrosis* is referred to as *erysipeloid*. (This condition should not be confused with the erysipeloid of Rosenbach.) The eruption is seen on the abdomen and thighs spreading from there with an erythematous circinate flush and tender border. There may be recurrent attacks¹¹⁵⁴ with occasional abscess formation¹¹⁵⁵.

The complexion of patients suffering from *contracted kidney* is often yellowish. This discoloration is restricted to parts exposed to light. The pigmentation is explained¹¹⁵⁶ by the retention of urochromogens which under the influence of light change into their color just as they do in a pale urine from an arteriosclerotic kidney. There is no retention of urochromogens in acute nephritis.

¹¹⁴⁸Sachs H. Erythema exsudativum multiforme und Erkrankungen innerer Organe. Arch f Dermat u Syph 23 357 1899.

¹¹⁴⁹Du kworth D. A Case of Chronic Interstitial Nephritis in Which Dermatitis Exfoliativa Supervened. Br J Dermat 12 1900.

¹¹⁵⁰Phoma N. Erythema exsudativum multiforme. In: Erythema exsudativum multiforme. Leiden. Hall 1924. Carl Marhold.

¹¹⁵¹Kri tanof S. A. La réaction de la peau à la filtration des reins. Ann de dermat et syph 7 685-61 1936.

¹¹⁵²Aldrich C. A. and Boyle H. H. Erysipelas Like Lesions of Skin in Nephrosis. Am J Dis Child 55 10 1934.

¹¹⁵³Howard H. and Kohn J. L. Bacteremia and Skin Manifestations of Lipoid Nephrosis. Am J Dis Child 35 627-4 1939.

¹¹⁵⁴Beck E. Untersuchungen über das Zustandekommen der gelblichen Hautfärbung bei Nephritis. Münch med Wochenschr 77 19 1930.

Carotinemia is always present in nephroses but only in 10 per cent does the skin become noticeably yellow¹¹⁶⁷

In acute nephritis the *capillaroscope* may reveal narrow arterial and wide tortuous venous segments. The subpapillary venous plexus is well visible and the circulation is slowed. These changes may precede the outbreak of nephritis¹⁷⁰ (Goth after Niekau¹¹⁶⁸) suggesting the primarity of the capillary damage.

Herpes zoster has often been seen in attacks of *nephrolithiasis*¹¹⁶⁹. Severin¹¹⁷⁰ found that these eruptions corresponded to the eleventh and twelfth dorsal and the first and second lumbar segments. Their area was found identical with the associated Head zones. Some cases of *pruritus* and *obstinate eczema* in chronic nephrolithiasis were relieved by operation. They can be interpreted as caused by the infected focus and by parenchymal damage caused by calculi and infection.

Pruritus is a common symptom in all types of chronic urinary retention. Thus it is frequently and early observed in benign hypertrophy of the prostate and occurs also in stricture of the urethra. It is good advice to examine prostate and bladder in all unexplained cases of pruritus and secondary pyoderma present in elderly men.^{1171, 1172} In rare instances pruritus vulvae may be caused by nephropoiesis.¹¹⁷³

Though not being the cause of dermatoses *Peyronie's disease* or induration of the tunica albuginea of the corpora cavernosa penis is possibly a manifestation of a systemic disorder which may also cause surface symptoms. Tournine and Ruel¹¹⁷⁴ call hereditary polyfibromatosis the tendency to form nodular nonencapsulated indurations in many parts of the connective tissue. While the association of induration of the corpora cavernosa with Dupuytren's contraction of the palmar aponeuroses has long been recognized keloids, fibromas of the fingers and similar connective tissue lesions are also seen together with Peyronie's disease. Simple dominant heredity is supposed to exist. Similar hypotheses of earlier authors have not found acceptance.¹¹⁷⁵

¹¹⁶⁷Boeck W. G. and Vater W. M. Xanthemia and Xanthosis (Carotinemia). *J. Lab. & Clin. Med.* 11:29, 1143, 1919.

¹¹⁶⁸Lutz W. Stoffwechs. Fund. Haut. Handb. d. H. u. G. 2, 1929.

¹¹⁶⁹Strickler A. Proctitis of the Kidney as a Cause of Pruritus Vulvae. *Arch. Dermat. & Syph.* 80: 405, 1914.

¹¹⁷⁰Tournine A. and Ruel H. Hereditary Polyfibromatosis. *Ann. de Dermat. & Syph.* 5: 15, 1915.

¹¹⁷¹Nedetzki W. Dupuytren'sche Kontraktur und Herpes. *Arch. f. klin. path. u. Gew. r. Hyg.* 2: 3-43, 1937.

CHAPTER XVI

DISORDERS OF THE ENDOCRINE GLANDS

THE PITUITARY BODY

The hormones of the *anterior lobe* of the pituitary stimulate the activity of the thyroid the parathyroids the mammary glands the islands of Langerhans in the pancreas the adrenal cortex the gonads and the placenta. The carbohydrate and fat metabolism and the growth are influenced either directly or indirectly by the effects on the above named glands ^{116 117}

The *intermediate lobe* activates the melanophores in the skin of amphibia. Its physiology in man is little understood.

The *posterior lobe* secretes two principles which act on the smooth muscle fibers. It profoundly influences diuresis by the production of an antidiuretic hormone.

Frohlich's Syndrome

Dystrophia adiposogenitalis or *Frohlich's Syndrome* is the triad of obesity, particularly of the lower trunk genital underdevelopment and pituitary symptoms. The latter seem due to hypoactivity of the anterior lobe and the pars intermedia. Frohlich's Syndrome is one of the commonest endocrine diseases especially of young males. This was demonstrated in the induction centers during the last war ¹¹⁸

Dermadromes — In the younger patients the skin is smooth and pale and the veins are well visualized. Cushing remarks that persistent freckles on exposed areas is a characteristic of most cases of hypopituitarism. Perspiration is scant or lacking ¹¹⁹. The subcutaneous fat which is particularly abundant on the hips sometimes seems to suggest a deep seated nonpitting edema. Striae are seldom seen. The pubic and axillary hair is absent and the lateral third of the eye brow is often missing. Ordinarily the scalp hair is not only unaffected but seems to be especially well developed. If the under-developed gonads start functioning e.g. after successful treatment with anterior pituitary hormone the body hair and the other secondary sex characteristics may still develop. Several authors emphasize the small thin under-developed nails which do not show lunulae at their bases. Onychogryphosis fragility of the nails and opaqueness of the nail substance have occasionally been noticed.

¹¹⁶ Leitch, E. L. *Practical Therapeutics General Practice* Chicago Ill. 1940 Year Book Publishers Inc.

¹¹⁷ Rynearson, F. H. *Hormones of the Anterior Lobe of the Pituitary Body* J. A. M. A. 125 5 1944

¹¹⁸ Rowntree, J. *Endocrinology* 17 1000-1000 in *Annals of the Royal Society of Medicine* 4 545-546 1944

¹¹⁹ Cushing H. *The Pituitary Body and Its Disorders* Philadelphia 1911

In the rare *Laurence Moon Biedl* syndrome which consists of dystrophia adiposogenitalis retinitis pigmentosa mental deficiency and polydactylism cutaneous peculiarities other than in Fröhlich's syndrome have not been recorded.

L. Frankel noticed the failure of the lateral parts of the escutcheon to develop in patients with *pituitary infantilism*. (After Mussio Fournier¹³)



Fig. 164. Fröhlich's type. Male aged 15 years. Obesity gynecomastia fall of pubic hair.

The complete absence of secondary sex characteristics dryness of the skin freckles and hypotrichosis of body and scalp is the rule in *dwarfs of pituitary origin* (Type Lorain Levi). The scalp loses some or much of its hair mostly in the vertex area less so at the margins. This vertex type of alopecia has been observed in several pituitary conditions. (Engelbach). *Cutis lara* and *Ehlers Danlos syndrome* has in some cases been related to hypopituitarism.¹⁴

Cachexia Pituitaria Simmonds's Disease

Simmonds Disease occurs almost exclusively in women after childbirth. The cause is atrophy or destruction of the glandular part of the pituitary.

The early stages of this syndrome resemble myxedema. Later with increasing wasting amenorrhea or in the male impotence develops. Muscular weakness extreme loss of fat hypotension apathy and hypersomnia low temperature low blood sugar low basal metabolism and eosinophilia compose a picture which can easily be confused with other cachectic conditions. Good and sometimes dramatic results have been obtained with anterior lobe extracts.

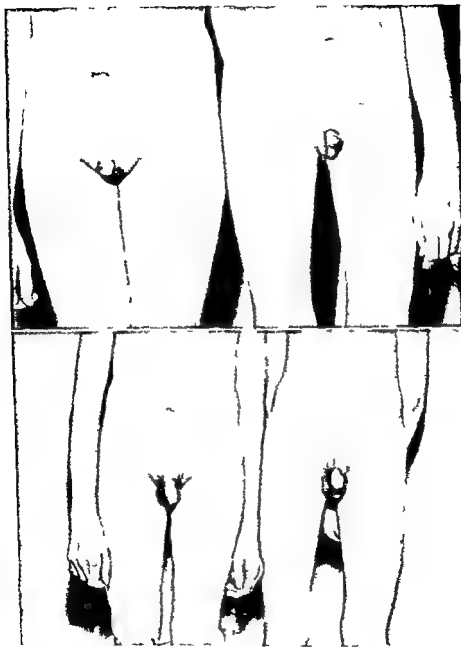


Fig. 165.—Brothers aged 24 and 27 years. Arrested sexual development at the age of 14. Froehlich type. Almost no pubic hair obesity before after one year of treatment with gonadotropic hormone and testosterone. (Courtesy Wisconsin General Hospital.)



Fig. 100—Lawrence-Moon-Bell syndrome. Note polydactyly. (Courtesy Wisconsin Central Hospital.)

Dermadromes—The skin is waxy, pale or yellowish and slightly edematous. Later the turgidity disappears and the skin becomes dry, wrinkled and slightly caly or in some areas especially about the hands and feet glossy, chilblain like or even clerodermatic. There is a definite tendency toward pigmentation. The pubic and axillary hair as well as the eyebrows and beard disappear completely in the fully developed syndrome.^{1166 1170} In some instances not a single lanugo hair can be detected on the whole body surface. The eyelashes and the scalp hair usually stay. The nails and teeth fall out or suffer dystrophic changes.¹¹⁷¹

Acromegaly

Acromegaly is caused by hyperactivity of the eosinophile cells of the anterior pituitary which are responsible for the growth stimulating hormone. Eosinophile (acidophile) tumors and eosinophile hyperplasia have often been found.

The overgrowth affects the skeleton and other systems. Maxillary rather than mandibular prognathism is characteristic of the true acromegalic. The nasolabial folds deepen and the ears seem to be set back. The teeth become separated and the hands and feet enlarged. The viscera take part in the unnatural growth. The hyperfunction of the anterior pituitary may be followed by hypo-

¹¹⁶⁶B. H. H. W. Zur Internal J. Simon 1. n. k. a. kl. It. Fat. klin. logie 16 309 1934

¹¹⁶⁷Di. Simmondsche Krankheit. Imfrag. M. J. H. 32 89 89 93 1947 1236

¹¹⁶⁸Zollha. J. Dermat. J. G. H. B. i. hu. k. J. Immo. 1. ch. Lett. n. H. K. gyogy. 92 ml. 17 1 193. Z. H. 33

¹¹⁶⁹Cost. ntini. F. C. ntref. ut. H. i. o. alla. me. z. i. H. a. malattia. H. Sin. n. i. (ca. h. e. i. i. p. o. s. s. a. r. i. a.) J. H. H. i. r. o. z. med. 38 1 04 1911

¹¹⁷⁰H. ma. h. H. r. k. H. k. J. Simm. n. tsch. J. r. a. k. H. It. M. B. et. med. Weh. wehr. 77 1620 1930

¹¹⁷¹Graul. n. r. W. Di. hypophy. dr. k. a. h. i. Sim. J. sch. J. r. a. k. H. It. Ztsch. f. kl. Med. 101 19 19

function and incomplete regression of the acromegalic signs in the soft tissues¹¹⁶ Such a regression in the skeletal system is hardly possible. Therefore the typical cutaneous signs of acromegaly may be absent in fully developed skeletal acromegaly.



Fig. 167.—Acromegaly. Not frank malformation, deepening of furrow especially nuchal and nasolabial fold. Ears not too big. (Courtesy Wisconsin College Hospital.)

Dermadromes—In acromegaly the skin like the bones and the viscera is overdeveloped in every direction and can be compared to a normal skin under a magnifying glass. The surface is coarse, the furrows deepened and the connective tissue thickened or somewhat edematous. Moles may appear or existing ones grow. Combination with Recklinghausen's disease has been observed a number of times¹¹⁷. The cutaneous glands are enlarged and their hyperactivity is indicated by moisture and seborrhea. Comedones and follicular keratosis are marked. Acne is not uncommon. The pigmentation is moderately accentuated^{118, 119}. The hair growth is increased in about one fourth of the cases occurring^{116, 120} especially on the body, so that in women a more masculine habitus results. In only seven per cent does the hair growth decrease¹¹⁴. By feeding young rat or injecting young dogs with anterior lobe extract the hair has been shown to become thicker than in the control¹¹⁴ (Robertson 1917 after Muir).

¹¹⁴ Atkinson, F. H. B. Acromegaly. From a study of the literature. 1931-1934. *Endocrinology* 21: 370-386.

¹¹⁵ Atkinson, F. H. B. Acromegaly. London, 1933. John Bale & Danielsson Ltd.

¹¹⁶ Brown, A. W. A. Illness of the Human Skull. *Journal of the Royal Society of Medicine* 12: 40-3, 1919.

¹¹⁷ D. H. H. L. M. Acromegaly. 100 Cases. *Journal of the Royal Society of Medicine* 12: 40-3, 1919.

¹¹⁸ Deutsch, F. Induced (Experimental) Feeding Upon Growth and Sexual Development. *Bull. Joliet Hospital* 27: 29-42, 1919.

Fournier¹⁵) Occasionally blond hair becomes darker and straight hair becomes curly and negroid¹¹⁷ The scalp hair may become thin on the vertex¹¹⁸ and premature greying may be seen The nails participate in the general hyper trophy becoming broad striated sometimes spoon shaped (coilonychia)¹⁹



Fig 168

Fig 169

Fig 168 Cushing's syndrome Broad purplish striae obesity (Courtesy Wisconsin General Hospital)

Fig 169 Broad purplish striae in Cushing's syndrome (Courtesy Wisconsin General Hospital)

and occasionally long (Walker after Atkinson¹¹⁹) Varicose veins are not uncommon

*Cutis verticis gyrata*¹²⁰ is a congenital anomaly consisting of an excess of scalp which causes the skin of the vertex to form folds and furrows resembling

¹¹⁷Aschner B Der Einfluss der Hypophyse auf die weiblichen Geschlechtsorgane Med Klin 20 1911 1915 1916

¹¹⁸Friedrich W Hair Growth and Elimination M Clin North America 9 141 1915

¹¹⁹Jadassohn J Ein eigentümliche Furchung der Occipitalhäut am Hinterkopf 9th Kongr Deutsch dermat Ges Bern 1906

is often described as a full moon face but the facial expression is more painful than jolly. Weakness, kyphosis, back aches, amenorrhea in the female and impotence in the male are other symptoms.

Dermadromes—The most striking dermadrome is the development of broad purplish striae atrophicae mainly in the lower and lateral parts of the abdominal skin. They were present in all of Cushing's twelve cases and have since been seen in a great number of instances.¹¹⁸⁶ It seems as if the basophile adenoma produces a toxic substance with a special affinity to the elastic fibers. Their resistance and elasticity appear to be weakened so that they tear on relatively slight strain (see striae of pregnancy).



Fig. 171.—Cushing's syndrome. Livid punctularis. (Courtesy Wisconsin General Hospital.)

The skin is often hyperpigmented.¹¹⁸⁶ It is dusky or copper colored especially the face. It is usually dry. Purpura traumatica has frequently been observed.

Hypertrichosis of the face and trunk has been constantly found in females and preadolescent males.

Many secondary endocrine disturbances are on record such as those due to dysfunction of the thyroid and adrenals. Diabetes has been recorded.

The resistance against infections is lowered; this leads to frequent pyoderms. Infections are often the immediate cause of death.

¹¹⁸⁶Jonas: Cushing's Syndrome. Med. Klin. 1936:1:814.

CHAPTER XVII

DISORDERS OF THE ENDOCRINE GLANDS

THE THYROID GLAND

Thyroxin the hormone of the thyroid gland stimulates the oxidative processes of the body

The influence of the thyroid on the skin is manifold¹¹⁸ The removal of the gland in animals increases the content of water and chlorides the total nitrogen and the protein derivatives in the skin Administration of thyroxin decreases the cutaneous chlorides and the water and increases the sugar and nitrogen Some of these effects may be reversed with high doses of thyroxin Thyroidectomy increases the capacity of the skin to swell in 1/10 normal HCl (Quellung) Thyroxin causes higher and more prolonged skin and blood sugar tolerance curves The resorption time of a saline wheal is prolonged after thyroidectomy and shortened under the influence of thyroxin while the resorption of potassium iodide shows an opposite tendency Thyroxin increases the sensitivity of the skin to X ray and ultraviolet rays¹¹⁹

Hyperthyroidism (Grave's Disease, Basedow's Disease, Thyrotoxicosis, Exophthalmic Goiter)

The skin in hyperthyroidism is smooth thin and elastic with a velvety feel¹²⁰ This is in part a constitutional characteristic and is often present before any symptoms of the disease become apparent The skin is moist warm and rosy but the color is unstable The elevation of the temperature is roughly proportional to the increase in the metabolic rate The difference in temperature between covered and exposed skin areas is less pronounced than in a person with a normal metabolism It seems that the thinness of the skin as well as the increased temperature and moisture helps to free the body from a surplus of heat created by the elevated metabolism The patients usually complain of excessive warmth and like to sleep with the limbs uncovered

Dermadromes —Erythema of the chest and back and of the parts where the clothing presses is common¹²⁰ Unexpectedly the capillary microscope shows that the capillaries are thinner than normal¹²¹ although observations of enlarged

¹¹⁸Bohnstedt R M Experimentelle Untersuchung n über di Beziehungen zwischen Haut und in endokrinologisch in Syst m Arch f exp Path 176 475 1931 1935

¹¹⁹Filinger J Über die Bedeutung der Schilddrüse für di Ablauf d Strahlenreaktionen an der Haut Klin Wch schr 11 1019 1931

¹²⁰Joeman J H Changes in the skin i Thyrotoxicosis Am J M Sc 121 691-692 1931

¹²¹Joan F P Th Thyroid Springfield Ill 193 Charles C Thomas

¹²²Micha I M and Bu hke W Über das Verhalten d r Hautcapillaren beim Morbus Basedow Klin Wch schr 11 1022 1591 1937

capillaries have also been made¹¹⁹ Dilatation of the arterioles of the sub papillary plexus accounts for the increased rate of the peripheral blood flow and the high skin temperature (Bansi after Michael and Buschke¹¹⁹) Due to the increased moisture the electric resistance of the skin is low

Hyperhidrosis is often as marked and as weakening as in pulmonary tuberculosis^{119 1194} Seborrhea acne and comedos indicate overactivity of the sebaceous glands In about 50 per cent of the cases¹¹⁹⁵ there exists a tendency to increased pigmentation The hyperpigmentation is often inconspicuous this explains the much smaller percentages in some series Youmans¹¹⁹ sees a difference from the pigmentation in Addison's disease mainly in its lesser degree and in the lack of pigmentation of the mucous membranes The pigmentation seems to have the older authors more impressed than those of recent years¹¹⁹⁴ The hyperpigmentation of the eyelids is often regarded as suggestive of hyperthyroidism (Jellinek's sign)

Vitiligo has been seen in roughly 10 per cent of the cases^{1195 1196} This is high enough to warrant a basal metabolism test in all cases of vitiligo

There exists a marked tendency to transient edema Unexplained puffiness of the eyelids¹¹⁹⁷ and ankles chronic urticaria¹¹⁹⁸ and angioneurotic edema should cause the physician to think of hyperthyroidism The resorption-time of intradermally injected saline (McClure Aldrich test) has been found to be prolonged in untreated cases with a return to normal after operation or iodine treatment¹¹⁹⁸ The validity of these findings however has been disputed¹¹⁹⁹

Maranon's sign is the more marked and longer lasting red dermographism in the skin covering the thyroid gland as compared with the red dermographism in other areas The sign is frequently positive in hyperthyroidism but is not specific^{1 198}

The hair is very sensitive to the toxic effects of hyperthyroidism Sainton^{1 19} and his collaborators noticed diffuse or circumscribed loss of the hair in 43 per cent of their 180 cases The vertex and the temples are especially affected^{15 1 93}

¹¹⁹²Roberts E and Griffith J Q Jr Quantitative Study of Cutaneous Capillaries in Hyperthyroidism Am Heart J 14 594-607 1937

¹¹⁹³Michael M and Buschke W Das Verhalten der Hautkapillaren beim Morbus Basedow Deutsche med Wchnschr 59 134 135 1933

¹¹⁹⁴Hyde and McEwen The Dermatoecia in Exophthalmic Goitre Am J M Sc 125 1000 1903

¹¹⁹⁵Hamwell B Anemia and Diseases of the Blood-forming Organs and Ducts Gland 14, 99

¹¹⁹⁶Habermann H Paratypische Pigmentanomalien Ha db d H m Gk 4 2 706 934 1933

¹¹⁹⁷Dore Cutaneous Affection Occurring in the Course of Graves Disease Brit J Dermat 33 353 1900

¹¹⁹⁸Rouss J N Chronic Urticaria a Thyro-Adrenal Syndrome How to Interpret the Direction of the Dysfunction and What Type of Agent to Employ in its Treatment South M J 22 664-672 1919

¹¹⁹⁹Mora J M Intracutaneous Salt Solution Test in Thyrotoxicosis Am J M Sc 177 210 1919

¹²⁰⁰Efrussi R Le signe de Maranon et sa signification dans le goitre exophtalmique Thèse de Paris 1916

¹²⁰¹Sainton F and Simonnet H Les troubles de la fonction thyroïdienne et leur action sur le système pileux Ann de med 29 263 1931

¹²⁰²Sainton F and Simonnet H Hyperthyroïdisme provoqué par la thyroïdine synthétique chez un malade atteint d'un syndrome pharidolalulaire avec sclérotomie et cataract Bull et mém Soc méd hôp de Paris 43 1045 1917

¹²⁰³Forster H The Relation of Interrelations to Cutaneous Disease J Cutan Dis 34 1 1916

Typical *alopecia areata* is not infrequently associated with hyperthyroidism an observation already made by Basedow.¹⁰⁴¹⁰⁵ Alopecia as well as canities may affect the head hair the beard the eye lashes the eyebrows and the body hair. Some authors emphasize the frequency of alopecia of the lateral third of the eyebrows. White spots in the hair have often been recorded.¹²⁰⁶ Improvement of the hyperthyroid condition may be followed by improvement of the alopecia. Universal baldness as well as hypertrichosis are rare.¹²⁰⁷

Alopecia as well as canities has been experimentally produced in animals by feeding with human or animal thyroid or with thyroxin.¹⁰⁸¹⁰⁹

Melanization however has also been observed after thyroid feeding.¹¹⁰¹¹¹ Chickens are much better fit for these experiments than cats and rabbits.¹¹¹ The sudden production of alopecia and canities after mental shock and terrifying experiences which so far has not been well substantiated could be explained by sympathetic stimulation of the thyroid.¹¹³¹¹⁵

In thyroidectomized rabbits regeneration of plucked hair is delayed or absent.¹¹⁶¹¹⁷ Thyroid extract feeding speeds the regeneration of plucked feathers in pigeons.¹¹⁸

There is no relation between the severity of the hair changes and the severity of the hyperthyroidism. This refers to the clinical observations as well as to the animal experiments. The blood of thyroidectomized horses compensates the effect of thyroid feeding on the integuments.¹¹⁹ The extract of toxic goiter is reported to be more effective on the plumage of chickens than the extract of simple goiter.¹¹⁹

In spite of these and other suggestive experiments the etiology of *alopecia areata* has not been elucidated. It seems that many factors are able to produce

- ¹⁰⁴von Basedow G A. Exophthalmus durch Hyperphie des Zellgewebes in der Augnhut. Wechnschr f d ges Hthk. Berlin 1840.
- ¹⁰⁵Laboureaud H. Diagnostic et traitement des affections du cuir chevelu. Paris 1930. Masson & Co.
- ¹⁰⁶Pynt J. Dy trophies et dychromies des formations épidermiques au cours du syndrome de Basedow (Maladie de Basedow). Thèse Paris 1935.
- ¹⁰⁷Barbier W. D. Influence des sécrétions adocriniennes sur la pousse des poils. Rev. franç. d'Endocrinol. 3: 301-31. 1935.
- ¹⁰⁸Zavodovski. Effect of Single Doses of Thyroid Gland on Poultry. Endocrinology 9: 175-186. 1934.
- ¹⁰⁹Zadori M. Hormone und das Gefieder der Vögel. Endokriolog. 10: 336. 1932.
- ¹¹⁰Col and F. J. Melanization After Thyroid Feeding. J. Agricul. Research 22: 10-14.
- ¹¹¹Crow and Hunt. Melanization of Chicken Feathers After Thyroid Feeding. J. J. No. 9. 1930.
- ¹¹²Sainton P. Maimon M. and Maimon H. L'hyperthyroïdisme et son action sur les phanères. Bull. Soc. franç. d'Hygiène et Hyph. 11: 77. 1930.
- ¹¹³Lévy F. Les anomalies de la pigmentation. Rev. franç. d'Hygiène et Hyph. 11: 77. 1930.
- ¹¹⁴Lescaudron J. Les anomalies de la pigmentation. Rev. franç. d'Hygiène et Hyph. 11: 77. 1930.
- ¹¹⁵Ham J. Posttraumatische Alopecia areata. Zbl. 44: 5. 1933.
- ¹¹⁶Barbier W. Posttraumatic Alopecia areata. Proc. Roy. Soc. Med. 25: 975-976. 1932.
- ¹¹⁷Purja H. The Role of Physiology of the Endocrine Glands in the Pathogenesis of Alopecia areata. Biochem. Ztschr. 167: 43. 1934.
- ¹¹⁸Cooper Z. K. Endocrine Glands and Hair. Review of Literature. Arch. Dermat. & Syph. 21: 1007-1009. 1930.
- ¹¹⁹Larionov W. Th. Wolkewitz A. A. and Bily N. W. Die Regeneration des Gefieders der Tauben bei Verschiedenen humoralen Einwirkungen. Endokriolog. 11: 416-4. 1933.
- ¹²⁰Sainton P. Maimon M. et Barbier F. Action comparée des extraits de glande thyroïde de Basedow et de goitreux sur le plumage des gallinacées. Bull. Soc. franç. de dermat. et Syph. 27: 634. 1930.

the same typical picture which is more than twice as common in men as in women^{1 6}. Infection^{1 1 12} seems plausible in a number of cases. Hyperthyroidism as well as hypothyroidism^{12 3} has been seen too often in alopecia areata to be dismissed as a coincidental occurrence^{1 3 1 6}.

Fig 172

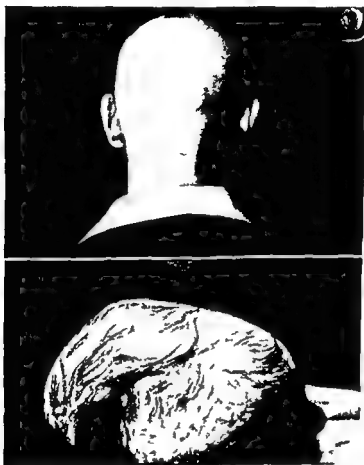


Fig 173

Fig 17 — Alopecia totalis. Moderate hypothyroidism.

Fig 173 — Same patient after treatment with thyroid.

¹²⁰Walsman M and Kepler E J. Alopecia Areata. An Appraisal of Endocrine Factors in Its Causation. J A M A 126: 2004-2006, 1941.

¹⁷¹Cederberg A. Untersuchungen über die Alopecia areata mit besonderer Berücksichtigung ihrer Ätiologie. Zeitschrift für klinische Medizin 47: 833-853, 1911. Zbl 40: 334.

¹⁷²Pitz R H. Zur Ätiologie und Symptomatologie der Alopecia areata. Arch. f. Dermat. u. Syph. 122: 264, 1929.

¹⁷³Throne B. Basal Metabolism in Dermatological Conditions. New York Stat. J. Med. 30: 50-65, 1930.

¹⁷⁴Šlihová V. Zur Pathogenese der Alopecia areata. Česká dermat. 12: 55-78, 1961. 107: 19.

135-141: 193. Zbl 42: 435.

¹²³Đoković. Alopecia areata multifocalis. Zbl 39: 142, 1931. 193.

¹²⁴Jeremijer. Alopecia areata mit bedingter Pigmentstörung. Zbl 41: 343, 193. 1933.

Waisman and Kepler¹⁰⁰ found a metabolic rate of less than minus 10 per cent in 25 per cent of their cases

The occasionally striking success of thyroid medication supports to some extent the thyroid etiology of some cases¹⁵ though the general stimulating effect of thyroid preparations has to be taken into account. A pituitary etiology has been claimed on the grounds of (1) supposed roentgenological changes in the sella turcica^{1, 5, 7} which was not confirmed by Waisman and Kepler^{1, 9} (2) coincidence with pituitary symptoms and (3) successful treatment with anterior lobe extracts^{100, 101} and radiation of the pituitary.^{8, 1, 32} There are some cases with ovarian, testicular and adrenal findings in alopecia areata with corresponding hormone therapeutic results. There are other arguments in favor of a pituitary etiology. Vitiligo or chloasma was present in about 10 per cent of Waisman and Kepler's^{1, 9} series. The influence of mental strain and shock is important. Preceding infections have also been accused.

The nails have occasionally been found altered in hyperthyroidism. Longitudinal and transverse grooves, atrophy, onycholysis and leukonychia have been described.

Hypothyroidism

However different the symptomatology of congenital and acquired thyroid deficiency may appear there is little difference in the dermatomes of both types. The dermatomes of hypothyroidism appear early and therefore they deserve particular attention.^{1, 33, 1, 35} It is necessary to emphasize that the fully developed syndrome is rare while cases having some of the symptoms occur quite frequently. Severe deficiencies of the thyroid have been observed with or without skin changes.

In hypothyroidism the skin is pale and often slightly yellowish due to carotenemia.^{1, 1, 33, 1, 36} It seems that the liver is unable to form Vitamin A from carotene due to the lowered metabolism. The skin is cool to the touch and the patient feels the cold more intensely than normal persons. The coolness of the skin is considered to be one of the earliest symptoms in the whole syndrome of hypothyroidism. The lowered temperature is especially noticeable in the ex-

¹⁰⁰Fell: Alopecia Totalis and Folliculitis Arch. Derm. & Syph. 29: 40, 1919

¹⁰¹Tsukada: Lebensstellung und Erfolg des Hypophysenhinterlappenhormons gegen Alopecia Jap. Dermat. pp. 339-339, 1933. Zbl. 45: 19, 1933

¹⁰²Hughes: B. N. Anterior Pituitary Therapy in Alopecia Totalis Clin. Med. & Surg. 40: 551, 1933

¹⁰³Tsukada: Antikörperbildung bei Alopecia areata in histopathologischer und klinischer Untersuchung Jap. J. Derm. & Urol. 1933

¹⁰⁴Whit: A. W. Histology of the Thyroid in Alopecia Canad. M. A. J. 21: 301, 1934

¹⁰⁵Trabach: Histologische Therapie bei endokrinen bedingtem Haarausfall Zbl. 23: 310, 1930

¹⁰⁶Pedersen: Chronische Thyroiditis und Rask. Vest. Dermat. 5: Nr. 4: 10, 1911

¹⁰⁷Knaus: Wirkung der Thyroidinbehandlung auf die Histologie Myxödemkinder. Histologische Untersuchung. A. J. Soc. Med. Duodecim 15: 1: 13, 1931. 71: 40, 630, 1932

¹⁰⁸Escamilla: R. F. Carotemia in Myxedema. Explanation of "Brightly Icteric Tint." J. Clin. Med. 2: 33-3, 1931

¹⁰⁹Mandbaum: T. Caudel: S. J. Millman: Hypothyroidism, Hyperlipemia and Carotenemia. J. Clin. Endocrinol. 2: 465-467, 1942

extremities where it is sometimes combined with acrocyanosis and associated complications like chilblains and tuberculids.¹³⁷ Several authors^{1238 1239} saw deep ulcerations of the legs connected with hypothyroidism and they advised treatment with thyroid by mouth and thyroid powder or thyroid salve locally. The skin is dry especially on the extensor surfaces of the extremities. In some cases of acquired myxedema marked keratosis palmaris and plantaris was observed and successfully treated with daily doses of 2 — 0.3 Gm of thyroid.^{15 133 1240 1241} The basal metabolism has often been studied in congenital ichthyosis. The findings and the results of thyroid therapy are controversial.^{14 144}

The dryness of the palms and arm pits (anhidrosis) is striking since the secretion of the sweat glands and of the sebaceous glands is reduced or completely absent. Nevi and moles may appear and desquamation is pronounced due to the dryness and to the tendency toward increased keratosis. In advanced or neglected cases this may cause a picture similar to ichthyosis particularly around the knees and elbows and also in the axillary and inguinal folds (Reuter in discussion to Cornbleet and Cohen¹⁴⁴). In some cases of congenital ichthyosis thyroid therapy seems to have given relief.^{126 1241} Itching is a frequent complaint.

The edema in fully developed myxedema is nonpitting and firm. It is most marked in the face and in the ears which sometimes have a cauliflower like appearance.¹¹⁸⁰ The facial features are coarse. The term eskimo face¹²⁴² is significant. Eyes and nose appear smaller than normal the latter especially in children is saddle shaped. This sign is commonly met with. The eyelids especially the lower lids the skin of the forehead the ears and the lips are swollen and cause a deepening of the nasolabial and forehead folds. The suprascapular fossae and the dorsa of the hands and feet are other sites of increased myxedematous or fat pads. The swelling may extend to the mucosae. The tongue the uvula and the nasal and laryngeal mucosae may become involved with a consequent disturbance of the voice. The thick protruding tongue of the cretin is a familiar picture.

- ¹³⁷Covisa and B Janaro. Tuberkulide and Hypothyroidismus. *Acta dermatol* 13 4 1921
Zbl 3 353
¹³⁸Coburn M H. Leg Ulcers Due to Thyroid Dysfunction. *JAMA* 102 283 1934
¹³⁹Eppinger H. Torpide Hautgeschwülste als Symptom inneren lokalen Myxedems. *Klin Wchnschr* 10 692 693 1931
¹⁴⁰Vissio Fournier J C. Kératodermie plantaire et palmaire chez une hypothyroïdienne guérie par la thyroïdine. *Bull et mém Soc méd Hôp de Paris* 48 1236 1237 1932
¹⁴¹Cervino J M Vertoll A and Larro A Higuera R A. Keratodermia of Hand and Feet and Thyroid Dysfunction. *Endocrinology* 22 615 1934
¹⁴²Krogh M and With G. On the Standard Metabolism in Ichthyosis. *Acta dermatol urol* 3 558 10 2 Zbl 9 50
¹⁴³Grünwald H W. Untersuchung über die Stoffwechsel bei Ichthyosis. *Arch f Dermat & Syph* 149 466-476 1925
¹⁴⁴Porter A. Basal Metabolism in Ichthyosis. *Brit J Dermat* 44 475-491 1926
¹⁴⁵Cornbleet Th and Cohen D. Pellagra and Myxedema. *Arch Dermat & Syph* 42 1140 1928
¹⁴⁶Leben H. Ichthyosis als Folge einer lokalen Störung. *Dermat Wchnschr* 44 710-712 193
¹⁴⁷Deusch G and Neuhaus G. Myxödem und Ichthyosis. *München med Wchnschr* 76 1661 1929
¹⁴⁸Janoušek J. Ichthyosis simplex. *Jap J Dermat & Urol* 44 107 1934
¹⁴⁹Prader L F. Ein Fall von chronischer Insuffizienz der Thyreoidea. *Ein Beitrag zur Pathologie des Ödems*. *Czech J Dermat* 12 233 1931 Zbl 29 72

Increased pigmentation especially on the forehead around the lids and some distance from the mouth occurs. Severe bronze colored pigmentation of the body has been observed in cachexia thyreopriva¹²⁵¹. However it is doubtful whether or not the pigmentary changes are caused by the hypothyroidism. Curschmann¹ infrequently found grey hair in adult patients. He relates this finding to his observation that adult patients with chronic myxedema due to their lowered metabolism age later than normal persons. This author found patients with compensated myxedema at the age of sixty and seventy years look like forty five. Other authors frequently found premature greyness in myxedema¹².

Loss of hair is common in hypothyroidism. This clinical observation is supported by observations on thyroidectomized animals. The hair in myxedematous patients is dull dry brittle and easily wears off and sheds. The axillary and pubic hair becomes scanty or absent¹⁵. The margins of the scalp tend to become bald. Bald spots not always of the common areata type occur and may respond well to thyroid therapy although this treatment is ineffective in the majority of the cases of alopecia areata. In women baldness of the forehead is sometimes striking.

The significance of the loss of hair of the lateral third of the eyebrows as a symptom of hypothyroidism especially in children (Hertoghes or Levy and Rothschild's sign) is not generally recognized. It is less pronounced in the Teutonic races with whom thinner eyebrows are considered normal.

In some cases of hypothyroid infantilism the lanugo hair persists in considerable strength but disappears with thyroid medication¹⁶.

The nails are often changed. Dystrophies have been found in some series up to 93 per cent¹²⁵². The size can be decreased the normal curvature absent and the nail may be very thin. Decrease in size brittleness longitudinal and transverse grooving defective lunulae and white spots in the matrix are common¹³⁰. The rate of growth is markedly reduced¹²⁵³.

The resistance to pyogenic infections blepharitis and erysipelas is low in myxedematous patients. The clinical appearance of the myxedematous skin is the result of edema and excess mucin in the epidermis degeneration of the collagen and elastic fibers and a sparse cellular infiltration about the vessels¹³⁴. The electric resistance of the myxedematous skin is increased^{135, 17}.

Circumscribed Myxedema

This not extremely rare condition is a paradoxical one (Trotter in disc to Freudenthal¹³⁶). It consists of pretibial circumscribed lesions which are

¹Kocher A. Di Pathol. d. d. r. Schilddr. XVIII Congr. inn. Med. Wiesbaden pp. 59-127, 1906.

¹²⁵¹Curschmann H. Zur Klinik und Pathophysiologie des Myxedems (In besond. re der gutartigen) in: m. pl. (t. n. Fo. me.) Deutsche Zeitschr. f. Nervenheilk. 98: 1-9, 1917.

¹²⁵²Jarrett A. M. Hereditary Occurrence of Hypothyroidism With Dystrophies of the Nails and Hair. Arch. Neurol. & Psychiat. 2: 9, 1919.

¹²⁵³Rutter M. J. Histopathology of the Skin in Myxedema. Arch. Dermat. & Syph. 21: 55, 1931.

¹²⁵⁴Freudenthal W. and E. Linauer. St. R. Myxedema pagulosum et anulare. Proc. Roy. Soc. Med. 33: 353-360, 1940.

myxedematous in appearance and histology but are in the majority of the cases associated with hyperthyroidism even with the fully developed syndrome of exophthalmic goiter. It seems as if in these cases some parts of the skin especially of the lower legs are unable to use the hormone which is offered in abundance.



Fig. 14



Fig. 15

Fig. 14—Circumscribed tuberos myxedema (Courtesy Division of Dermatology Department of Medicine University of Chicago)

Fig. 15—Myxedema tuterum (Courtesy Dr. M. J. Herlitz)

The lesions are hard nodules or tuberculous plaques of varying size sometimes covering both pretibial areas. They are symmetrical and may be normal in color yellowish pinkish or brownish. Inflammatory symptoms are mostly absent. The follicles are often dilated so that a pig skin or orange peel appearance results. The lesions are quite hard and nonpitting. Hypertrichosis within the lesion is another paradoxical feature which has been encountered.¹⁴ The sweat secretion within the myxedematous lesions is normal or absent.¹⁵ The tempera-

¹⁴Wright, W. Lokales Myxedema mit Hypertrichosis symmetrisch an beiden Unterarmen. *Arch. Klin. Exp. Derm.* 71: 42, 5, 1913.

¹⁵Ingram, J. T. Circumscribed Myxedema Associated With Hyperthyroidism. *Rev. Méd. Latino-am.* 25: 1-131, 1913; 71: 41, 1913.

ture may be much lower than in the normal skin.¹⁵⁸ On puncture a mucilaginous tenacious serum seeps from the wound. The microscope shows infiltration with masses and strands of mucin.

The major changes are found in the cuts. The connective tissue fibers are edematous and homogenized. Oval and stellate cells are cattered throughout.^{154, 159, 160} Treatment with thyroid or iodine has occasionally produced toxic symptoms. Thyroidectomy precipitated the outbreak of circumscribed myxedema in some cases but abolished it in others. Since this dermatosis causes little discomfort the treatment should be guided by the necessities of the general condition.¹⁶¹



Fig 111.—Myxedema tuberosum in a patient with hypothyroidism. (From Amersbach J. O. Arch Dermat & Syph 1944.)

Lichenoid umbilicated papular,¹⁶² tuberos plaque like and other varieties of discrete myxedema are known as the atypical myxedema of Jadassohn and Doessekker.¹ The connection with thyroid dysfunction is usually less obvious.

¹⁵⁸Caroff W. L. L. Atypisches Myxödem. Ned. Tijdschr. v. geneesk. 75: 4156-4169, 1931. Zbl. 39: 78.

¹⁵⁹O'Leary P. A. Localized myxedema of the extremities in association with hyperphalmitic. (Rev. Arch. Dermat. & Syph. 21: 5, 1933).

¹⁶⁰O'Leary P. A. Histology of the skin. Arch. Dermat. & Syph. 21: 330-331, 1930.

¹⁶¹Jadassohn J. & Doessekker W. Histopathology of the skin. Myxedema. J. Derm. 12: 192, 1924.

¹⁶²Doessekker W. Atypisches tuberoses Myxödem. Arch. f. Dermat. & Syph. 123: 76, 1916.

in this group than in diffuse or pretibial myxedema¹⁵⁵. The oral mucosa may be involved¹⁵⁶.

Temporary facial puffiness following subtotal thyroidectomy but different from the localized form of myxedema has been observed in nine cases¹⁵⁷. It seems to be a mild form of myxedema and responds to thyroid therapy.

The Parathyroid Glands

The hormone of the parathyroid glands is concerned with calcium metabolism. It maintains the level of ionized calcium in the blood and regulates the use of calcium for skeletal growth. The proper degree of nervous and muscular irritability and the viscosity and coagulation of the blood are also influenced by the presence of calcium.

Relations between the parathyroids and certain dermatoses have often been suspected (see scleroderma calcinosis) but our knowledge of the skin in hyperparathyroidism is meager and uncertain. Albright¹⁵⁸ in his work on hyperparathyroidism does not mention any skin changes and no mention is made in the review of 135 proven cases by Wilder and Howell¹⁵⁹.

Hypoparathyroidism

Extirpation of the parathyroids was in a number of cases followed by the outbreak of a severe and characteristic dermatosis clinically identical with impetigo herpetiformis (Hebra). Since other symptoms of insufficient parathyroid activity especially tetany have been found in spontaneous cases of impetigo herpetiformis it seems justified to regard this disease as a dermatome of hypoparathyroidism.

Impetigo Herpetiformis—Hebra¹⁶⁰ in 1872 and shortly after him Kaposi¹⁶¹ first described the clinical picture of this disease and it has been but little changed since. The dermatosis starts with crops of pustules which often appear during pregnancy but sometimes in women without relation to pregnancy or in men. The primary lesion is a true pustule i.e. a vesicle filled with pus from the beginning and has a red and swollen base. These pustules are the size of a pinhead and are superficially seated in the epidermis being grouped in clusters and lines. Confluent pustules in the center of such groups form a scab (impetigo) while new pustules develop at the periphery and the center heals under the scab forming rings and polycyclic figures.

These eruptions may cover large areas sometimes the whole body surface. The navel, the genital and inguinal areas, the armpits and the submammary

¹⁵⁵Thompson and Thompson: Temporal Edema of the Face Following Treatment for Exophthalmic Goiter. *Am. J. Med. Sc.* 278: 73, 1929.

¹⁵⁶Albright: F. *Aub. J. C.* and Bauer: W. Hyperparathyroidism. *J. A. M. A.* 102: 1276, 1937.

¹⁵⁷Wilder H. M. and Howell L. P.: Etiology and Diagnosis in Hyperparathyroidism. *A. Rev.* 10 of 135 Proven Cases. *J. A. M. A.* 106: 427-431, 1936.

¹⁵⁸Hebra F.: Ueber einige in der Schwangerschaft und bei Uterinalkrankheiten vorkommende Hautkrankheiten. *Wien med. Wchnschr.* 187.

¹⁵⁹Kaposi M.: Impetigo herpetiformis. *Arch. f. Dermat. & Syph.* 29: 973, 1897.

regions are usually first and most severely involved. Deep ulceration has not been seen. Sometimes the mucosa shows lesions analagous to those of the skin. Crops of new pustules are often accompanied by chills and fever. Nephritis, splenomegaly and cachexia are the rule in fully developed cases which may take on the aspect of generalized exfoliative dermatitis. Itching is not a dominant symptom.

Impetigo herpetiformis is a severe and often fatal disease. Of the thirteen patients with impetigo herpetiformis reported by Kaposi^{1 67} from 1872 to 1884 twelve died from the disease. Glavécke^{1 68} (1896) found a mortality of 80 per cent among 20 cases from the literature. During the last twenty years relatively many nonfatal cases have been reported.

This disease is so rare that many dermatologists have never seen it. The great interest which it aroused is due to the fact that it is a characteristic dermatosis with a definite endocrine relationship. Hebra¹⁶⁶ and Kaposi^{1 67} who saw more cases than any other writers were convinced that impetigo herpetiformis is a disease of pregnant women. Later on Kaposi described a case in a man and more recently several cases in nonpregnant women, in children and in men^{1 69} have been presented.

In 1921 Schardorn¹⁷⁰ reported two cases of impetigo herpetiformis and tetany in nonpregnant women who only three days before had been subjected to thyroidectomy. Both women died and at autopsy no parathyroids were found. If there was any doubt about the part the operation played in the etiology it has been removed by the publication of at least nine more cases following thyroidectomy.^{171 172} In a case published by Kolisch¹⁷³ tetany followed thyroidectomy. The patient later became pregnant and developed impetigo herpetiformis. On the other hand it is surprising that impetigo herpetiformis has not been seen more often among the many cases of total thyroidectomy. Kocher^{1 61} e. g. in his famous paper in 1906 does not mention impetigo herpetiformis as a symptom of cachexia following total strumectomy.

The spontaneous cases in pregnancy are often but not always associated with symptoms of hypoparathyroidism. Osteomalacia, tetany,^{1 74 1280 1281} low

¹⁶⁶ Glavécke: Impetigo herpetiformis Arch f Gynaek 82: 1434 1896

¹⁶⁷ Kaposi A. F.: Impetigo herpetiformis. Mal Arch f Dermat u Syph 88: 10 117 1914

¹⁶⁸ Schardorn: Impetigo herpetiformis Arch f Dermat u Syph 132: 104-110 1911

¹⁶⁹ Lutz: Impetigo herpetiformis Dermat Ztsch 63: 384-390 1919

¹⁷⁰ Schardorn: Dermatologische parathyreopriva und dem Bild der Impetigo herpetiformis Zbl 39

13: 1031

¹⁷¹ Hartmann J.: Zu krit. logisch. Therapie der Impetigo herpetiformis Arch f Dermat u Syph 175: 93 106 1937

¹⁷² Wl. f. D. matit. herpetiformis Appearing Three Week After Thyroidectomy Arch Dermat u Syph 127: 537 34 1933

¹⁷³ Kolisch: Impetigo herpetiformis and Cu. With A. T. 10 (Dihydroxyterin) H. H. J. Med. H. H. 33: 1500 1937

¹⁷⁴ Schubert M.: Impetigo herpetiformis. A. T. 10 Th. r. ple. D. mat. Wchnschr 102: 761 1936

¹⁷⁵ Danisch F.: Impetigo herpetiformis postoperativ Tetani n. parathyreopriva Nachst. Fra. kfurt Ztschr f Path 33: 208 1919

¹⁷⁶ W. rth m. s. A. Lel. Impetigo herpetiformis Hebra Arch f Dermat u Syph 157: 214 33 1919

¹⁷⁷ Kolisch F.: Impetigo herpetiformis Zbl f Gyn 48: 90 1919

¹⁷⁸ Papf. r. e. l. her. Impetigo herpetiformis und Schw. z. Nachst. Zbl 21: 319 1914

¹⁷⁹ Less. ynaki: Impetigo herpetiformis Zbl 48: 59 1933

serum calcium^{121, 122} and cataract¹²³ have been observed with impetigo herpetiformis in pregnancy but a considerable number of cases have been found free of all such symptoms. This together with the nonobligatory occurrence after parathyroidectomy suggests that hypoparathyroidism is only one of the pathogenetic factors. In which direction other factors may be sought is indicated by cases with pituitary findings^{124, 125} mediastinal tumor¹²⁶ and dysfunction of the ovaries.¹²⁷ The possibility of an infection which only develops under certain circumstances cannot be denied though the lesions and the blood have almost always been found sterile. Italian authors have lately suggested virus infection



Fig. 177. Female aged 19 yrs. Chronic infection of all parts of the tongue with *Vibrio cholerae* in a case of (1) hypocalcemia and (2) hypoparathyroidism. (Courtesy of Dr. J. W. Wilson in the *Journal of the American Medical Association*.)

under certain hormonal and toxic conditions.¹²⁸ The clinical similarity to pustular psoriasis must be mentioned since hypocalcemia seems to be an etiologic factor in this dermatosis also.

The impetigo herpetiformis of pregnancy brings up the question of the artificial termination of the pregnancy in the case of this disease. Several dermatologists feel that this procedure is justified. However the disease not infre-

¹²¹Carter H and Lasek H I. Impetigo herpetiformis (ectopic eruption) during pregnancy. *Am J Obst & Gynec* 33: 114 (1937).

¹²²Koch A C. Hypocalcemia. *Arch Int Med* 49: 179-183, 1979 (1910).

¹²³Tryb A. Beitrag zur Ätiologie der Impetigo herpetiformis. *Arch Int Med* 49: 177-183 (1910).

¹²⁴Buschke A. Impetigo herpetiformis. *Zbl Bakt* 25: 14 (1904).

¹²⁵Buschke A. Impetigo herpetiformis als Folge einer Störung der Schilddrüse. *Dtsch Med Wochenschr* 78: 633-634 (1902).

¹²⁶Zocchi G. Impetigo herpetiformis in gravidanza. *Riv Patologia* 5: 40 (1933).

quently starts in the later months of pregnancy when inducing labor in the presence of a widespread purulent skin infection is a dangerous procedure. Moreover the termination of pregnancy does not always influence the course favorably. In some cases the patients died from the dermatosis during the puerperium. Nevertheless if the diagnosis is made early the pregnancy should be terminated and future pregnancies prevented.^{13 138}

There have been almost as many methods of treatment tried as cases recorded. Blood transfusions¹²⁸⁹ injections of normal serum and of serum of normal pregnant women^{130 131} estrogenic hormone (Buschke) and X ray sterilization¹³ have been used. Sulfanilamide accomplished a spectacular recovery in one recent case.¹³² Calcium in large doses¹³³ should always be given. In tetany Sevringhaus¹¹⁸ advises the oral administration of a 35 per cent solution of calcium chloride in a sweet vehicle one to two teaspoonfuls three times daily. The medicine is given one half hour before meals with plenty of water. Parathyroid extracts are unreliable. Dihydratachysterol¹³⁴ a derivative of ergosterol also known as A T 10 is more promising. There are a number of favorable reports on record.^{135 136 137 138 139 140} The dose is five to twenty drops of the oily solution daily.¹⁴⁰ A T 10 is so far the best substitute for the parathyroid hormone. It increases the phosphorus excretion and raises the calcium level of the blood.

Parathyroid insufficiency seems to increase the susceptibility to *chronic monilia infections* of the hands and nails.¹⁴⁰

Brittleness of the nails and hairs together with hyperhidrosis and Addisonoid hyperpigmentation is occasionally associated with hypoparathyroidism.^{13 1217}

The Thymus

Status thymicolymphaticus of the adult is a much disputed condition. The beard and body hair has been described as scanty and there often is a female configuration in men.¹²² Scantiness of the beard and of the axillary and pubic hair in both sexes with heterosexual distribution is part of Timme's syndrome which is a chronic multiglandular benign condition with pituitary gigantism, low blood pressure, low blood sugar and other features.¹²²²

¹²⁸⁹Buschke A. and Cuth W. Die Behandlung der Cravidität der mütterlichen für die künstliche Int. brechung. J. f. s. h. w. g. r. w. h. f. M. h. n. med. Wch. chr. 78 361-364 19 9

¹³Sch. r. h. e. M. Zu lichen. d. d. r. Impetigo herpetiformis der v. m. h. l. e. n. Pemphigusform: n. u. n. i. g. w. i. s. s. e. n. t. e. h. e. h. a. f. t. r. m. u. l. t. i. f. o. r. m. e. r. F. r. y. t. h. m. S. t. u. t. t. r. a. n. f. l. o. n. i. n. d. e. r. D. r. m. a. t. o. l. o. g. i. e. W. i. n. n. i. W. e. h. s. c. h. r. 80 717-720 760-6 801 00 1970

¹³⁰Rot. o. u. Impetigo herpetiformis. F. h. l. 33 349

¹³¹R. t. o. u. L. Zu lichen. d. d. r. Impetigo herpetiformis. D. r. m. a. t. W. h. s. c. h. r. 81 1059 1063 1970

¹³²G. r. u. t. z. Impetigo herpetiformis. F. h. l. 36 710

¹³³F. r. a. n. L. J. Impetigo herpetiformis. Arch. D. r. m. a. t. & G. y. p. h. 40 753-754 1939

¹³⁴H. o. l. t. z. J. N. ben. ch. l. i. d. r. n. i. n. u. s. s. i. n. D. u. t. a. r. h. m. e. d. W. e. h. s. c. h. r. 85 750-6 1939

¹³⁵S. r. h. e. G. Zu lichen. d. d. r. Impetigo herpetiformis. W. i. n. n. i. m. e. d. W. e. h. s. c. h. r. 86 15 1976

¹³⁶S. u. t. p. h. i. n. A. A. l. l. r. i. g. h. t. J. and M. C. u. e. H. J. F. i. v. C. a. s. e. s. (T. h. e. i. n. S. i. l. l. i. n. g. s.) of Idiopathic Hypoparathyroidism Associated with Moniliasis. J. C. l. i. n. F. a. c. i. e. n. c. i. a. 2 62-63 1943

¹³⁷F. m. r. o. n. H. S. t. a. t. u. s. L. y. m. p. h. a. t. i. c. u. s. i. n. A. d. u. l. t. s. Arch. I. n. t. M. e. d. 23 169 1914

¹³⁸W. i. f. W. E. n. d. o. c. r. i. n. o. l. o. g. y. I. M. o. d. e. r. n. P. r. a. c. t. i. c. e. I. l. l. u. s. t. r. a. t. i. o. n. 1976 W. B. S. a. u. n. d. e. r. s. C. o. m. p. a. n. y.

Carcinoma of the thymus has been seen to produce Cushing's syndrome in at least 3 cases^{1399 1400} The juvenile Hercules syndrome of precocious puberty in the male was seen in a case of mediastinal tumor probably a thymus lesion¹⁴⁰¹ Most thymomas do not provoke dermatomes

Deficiency of the thymus has by several authors been thought to be a cause of *psoriasis* The hypothesis was based on therapeutic results with injections of thymus extract¹⁴⁰² and stimulating doses of roentgen radiation directed to the upper sternal region^{1404 1405} Little has been heard of the subject during the last fifteen years

¹³⁹⁹Leyton O Turnbull H M and Bratton A H . Primary Cancer of the Thymus With Pluri-glandular Disturbance J Path & Bact 34 635 1931

¹⁴⁰⁰Duguid J B and Kennedy V M . Oat-cell Tumors of Mediastinal Glands J Path & Bact 33 93 1930

¹⁴⁰¹Thompson A W and Elshardt L . Cushing Syndrome J Clin Endocrinol 3 44-4 1943

¹⁴⁰²Weber M P and Wohl M . Macrogenitosomia of Juvenile Hercules Type With Tumor in Superior Mediastinum M Pre v 211 22 26 1944

¹⁴⁰³Samberger J . Ueber das Wesen der Psoriasis Acta dermat venerol 2 359 1911

¹⁴⁰⁴Brock W . Beziehungen der inneren Sekretion zur Schuppenflechte und deren Behandlung mit Thymusbestrahlung Strahlentherapie 11 573 604 1935

¹⁴⁰⁵Brock W . Psoriasis und ihre Secretion Deut che med Wchnschr 47 1420 14 2 1911

CHAPTER XVIII

DISORDERS OF THE ENDOCRINE GLANDS

THE ADRENAL GLANDS

The adrenal cortex through its hormone cortin is concerned with water mineral and carbohydrate metabolism¹³⁰⁶. It keeps up the muscular strength and it has important functions in pregnancy and lactation. Androgenic substances which are able to masculinize the appearance of females are produced in the adrenal cortex or in its neoplasmas. The medulla of the adrenal glands produces adrenalin which besides other effects stimulates the sympathetic system and inhibits the vagus. Destruction of the adrenals is fatal.

Addison's Disease

Addison's disease¹³⁰⁷ starts insidiously usually in middle life. Progressive asthenia and muscular fatigability, hypotension, epigastric pain, anorexia, morning sickness and other gastrointestinal symptoms may after long periods of relative mildness suddenly increase and give rise to an acute condition known as Addisonian crisis. Hyperpigmentation of the skin is an outstanding symptom. Dehydration, decrease in the sodium and chlorine concentration in the blood, increase in the blood potassium and nonprotein nitrogen (urea) and hypoglycemia are important findings especially during the crisis. The urinary sodium chloride is high. Sugar may occur in the urine in spite of the hypoglycemia¹³⁰⁸. The blood viscosity is high. Anemia is marked. The elimination of water after a sudden large intake of water is delayed. A water test designed by Robinson, Power and Kepler¹³⁰⁹ together with blood and urine chemistry has lately been shown to be of great diagnostic value¹³⁰⁹. The course is almost always fatal but with modern treatment health may be restored to such a large measure that cure may seem to be accomplished yet sudden death may occur from trivial causes¹³¹⁰. The cause of the syndrome is destruction of the adrenal cortex due in 9 out of 10 cases to tuberculosis.

¹³⁰⁶Goldfarb M. A. The Adrenal Gland in Health and Disease. Philadelphia 1944. F. A. Davis Company.

¹³⁰⁷Addison T. A Collection of the Published Writings of the Late Thomas Addison on the Constitutional and Local Effects of Disease of the Suprarenal Capsules. New Sydhams Society 1869. Reprinted in Rowntree and Scott. Addison's Disease. Philadelphia 1931. W. B. Saunders Company.

¹³⁰⁸Robinson F. J., Power M. H. and Kepler E. J. Addison's Disease—Diagnosis. Proc. Staff Meet. Mayo Clin. 18: 7-53 1941.

¹³⁰⁹Cutler M. H., Power M. H. and Wilder R. M. Concentrations of Chloride, Sodium and Potassium in Urine and Blood. Their Diagnostic Significance in Addison's Disease. J. A. M. A. 111: 117-122 1935.

¹³¹⁰Rowntree L. G. Report of 3 Cases of Clinical Addison's Disease Surviving More Than 15 Years. Endocrinology 26: 793-800 1940.

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¹³⁰¹Thompson A W and Eisenhardt L Cushing Syndrome J Clin Endocrinol **3** 445-4 1943

¹³⁰²Weber E P and Wohl M Macroorchitism of Juvenile Hercules Type With Tumor in Superior Mediastinum M Pre s **211** - 76 1944

¹³⁰³Hamberger J Ueber das Wesen der Psoriasis Acta dermat v venerol **2** 3 1901

¹³⁰⁴Brock W Beziehungen der inneren Sekretion zur Schuppenflechte und deren Behandlung mit Thymusstrahlung Strahlentherapie **11** 563-604 1900

¹³⁰⁵Brock W Psoriasis und innere Sekretion Deutsch med Wchnchr **47** 14 014 7 1901

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¹³⁰⁶Goldziher M A The Adrenal Gland in Health and Disease Philadelphia 1944 F A Davis Company

¹³⁰⁷Addison T A Collection of the Published Writings of the Late Thomas Addison on the Constitutional and Local Effects of Diseases of the Suprarenal Capsules New Sydenham Society 1869 Reprinted in Rowntree and Goldziher Addison's Disease Philadelphia 1931 W B Saunders Company

¹³⁰⁸Robinson F J Power M H and Kepler F J Addison Disease—Diagnosis Proc Staff Meet Mayo Clin 36 577-583 1941

¹³⁰⁹Cutler M H Fowler M H and White R M Concentration of Chloride Sodium and Potassium in Urine and Blood Their Diagnostic Significance in Addison's Disease JAMA 114 117-12 1935

¹³¹⁰Rowntree L C Report of 3 Cases of Clinical Addison's Disease Surviving More Than 1 Year Endocrinology 26 793-800 1940



Fig. 178—Addison's disease. Patient (left) with her sister for comparison. Discoloration only complaint so far. Patient died five months later.



Fig. 179—Addison's disease. Not pigmentation of exposed parts. (Courtesy Wisconsin General Hospital.)

Dermadromes—*Hyperpigmentation* of the skin in connection with destructive adrenal disease is in the vast majority of cases an early symptom often appearing before asthenia and fatigability. Pigmentation about the knuckles may be the first manifestation.^{131 132}

The fully developed discoloration is uneven in distribution and color. The face, neck, hands and other light exposed parts, the normally pigmented areas, the nipples, the linea alba of women who have been pregnant, the genital region, the gluteal fold and the umbilicus are usually affected first. All areas subject to



Fig. 180.—Addison's disease. Hyperpigmentation in linea alba and over prominent bones. (Courtesy Wm. H. G. Ralston, M.D.)

pressure, friction and irritation are apt to take on a darker color than the rest of the skin. Thus girdles, garters, shoulder straps, collars, collar buttons and bandages may leave indelible marks. The author saw a deaf woman who was wearing a hearing aid apparatus, the cord of which ran along her back. The slight pressure and friction of this cord had left a deep pigmented mark in the skin at a time when there was hardly any asthenia and little other pigmentation. The creases of the palms and the wrists are sharp dark lines, while the palms themselves are still light. Tight skin over bones is often hyperpigmented. Scars, e.g., vaccination marks, have a pronounced tendency to darken early in Addison's

¹³¹Rowntree, L. H. and Quinn, A. M. A Clinical Study of Addison's Disease. Phila. 1931. W. B. Saunders Company. p. 176.

¹³²Quinn, A. M. and Rowntree, L. G. Addison's Disease With Anomalous Pigmentation. Endocrinology 5: 303, 1929.

Fig 181



Fig 182

Fig 181 — Addison's disease. Pigmentation of palmar creases

Fig 182 — Addison's disease. Pigmentation of scars (flat iron burns)

disease Spillmann¹²³ advises to watch for the development of pigmentation after the application of an irritant plaster of mustard seed. Besides the unevenness caused by the various terrains great differences in the intensity of the pigmentation occur. In some cases the discoloration is blotchy in others irregular and ill defined. Some cases present patterns which look like a geographical map especially if much depigmentation accompanies the pigment increase. Thus pictures resembling vitiligo may ensue. True vitiligo has often been seen together with Addison's disease¹²⁴ and it is interesting that hypotension has been found in a number of vitiligo cases.



Fig. 183.—Addison's disease. Depigmentation and discoloration around the anus. White patient.

Leukoderma acquisitum centrifugum (Sutton's disease) and vitiligo have been seen in one case of Addison's syndrome¹²⁴. Some areas of the skin offer a marked resistance to the pigmentation. The narrow strip surrounding the lips often stays pale even in extremely dark pigmented cases. The same is sometimes true of the fingertips and nailbeds and the backs of the hands to a certain extent also of the eyelids. The circumoral strip often remains relatively white in other pigmentations as well for example in the form of discoloration which has been described by Poor¹²⁵ as *chloasma periorale virginum*.

The color of the Addison melanoderma is most commonly a tan¹²⁶ but may vary from slate amber or brown shades to the dark black of a full blooded Negro. This latter however is very rare. The depigmentation of the circum-

¹²³Spillman L. Dermatoses en rapport avec des troubles des glandes endocrines et de la nutrition. *Nouvelles Pratiques Dermatologiques* Vol. 5. Paris 1936. Masson & Cie pp. 68-71.

¹²⁴Obermayr & M. F. *Leukoderma Acquisitum centrifugum and Vitiligo in a Patient with Addison's Disease*. *Arch. Dermat. & Syph.* 35: 376, 1933.

PLATE III

- 1 Addison's disease Advanced case
- 2 Addison's disease Pigmented palmar creases
- 3 Addison's disease Pigmentation of the tongue
- 4 Addison's disease Pigmentation of the gum
- 5 Hemangioma of pregnancy Recurring in several pregnancies and receding spontaneously after childbirth (Patient of Dr J. Barroch.)
- 6 Leukosis vulvae multiple carcinomas



PLATE III

Fig 184



Fig 185



Fig 186



Fig 184 — A clinical photograph showing a close-up of a patient's face, specifically the mouth and chin area, with a dark, irregular lesion visible on the chin.

Fig 185 — A clinical photograph showing a close-up of a patient's face, specifically the mouth and chin area, with a dark, irregular lesion visible on the chin.

Fig 186 — A clinical photograph showing a close-up of a patient's face, specifically the mouth and chin area, with a dark, irregular lesion visible on the chin.

oral area and of the nailbeds is most striking in such cases. Jet black freckles are often seen mainly in areas exposed to light but even in unusual places like the palms and soles.¹²¹¹

The lips and the oral mucosa almost always show quite sharply outlined slate or bluish spots sometimes streaks. They resemble those seen in the mouth of the Negro. They appear rather early in the labial buccal or palatal mucosa sometimes on the tongue. The conjunctivae and the sclerae of the eyes as well as the vagina may participate in the general hyperpigmentation. Melanosis of the rectal mucosa has not yet been demonstrated. A number of cases of Addison's disease in the Negro have been recorded. Here the Addisonian pigment may be superimposed on the natural pigment so that the palms and soles become darker and an extremely dark color of the rest of the skin results.

Montgomery and O Leary¹²¹² emphasizes the relative softness of the skin which he relates to the flattening of the rete ridges and the thin but not atrophic epidermis. Sweating is often pronounced. Some believe the sweat to have a fishlike odor.¹²¹³ In prolonged cases the hair may become darker particular coarseness or hypertrichosis is denied.¹²¹⁴ Premature graying and scantiness of the hair has been observed in the course of the disease.^{1215 1217} The frequent shedding of the axillary and pubic hair is emphasized by Albright.¹²¹⁸ The nails may rarely take on a yellowish hue. Usually they stay pale.¹²¹⁹

Histopathology and Pathogenesis—The pigment is melanin and as such it is free of iron. It is accumulated in the tops of the basal cells of the epidermis. Dendritic chromatophores are also found in the cutis.¹²¹⁶ Bittorf¹²¹⁹ tried to explain the pigmentation in Addison's disease by assuming a higher oxidase content in the skin. His experiments with the skin of patients with Addison's disease were not confirmed by Bloch¹²²⁰ and his school who believed that not the increased oxidase content of the skin but an increased amount of melanogens accounts for higher melanin production. It was suggested that in the disturbed adrenals less tyrosin might be changed into adrenalin and thus more tyrosin might be available as a promelanin. Later (1928) Szent Gyorgy¹²²¹ who isolated vitamin C from normal adrenals advanced the theory that the high reducing power of this substance (then called hexuronic acid) serves as a control in the oxidation of promelanin to melanin in the normal skin. Its deficiency caused by destruction of the cortex would increase the oxidizing power of the skin and thus enhance the melanin formation which is an oxidation process. A great deal of experimental work seems to corroborate the antipigmentogenic role of vitamin C.

¹²¹¹ Montgomery H and O Leary I A. Pigmentation of the skin in Addison's Disease. Acanthosis Nigricans and Hemochromatosis. *Arch Dermat & Syph* 21: 970-994 1910.

¹²¹² Bauer Julius. *Ann Sekretion Berlin* 19: 7 Julius Spilng r.

¹²¹³ MacBryde C M. Addison's Disease. *Med Clin North America* 25: 391-400 1911.

¹²¹⁴ Albright F, Smith I H and Fraser R. Syndrome Characterized by Primary Ovarian Insufficiency and Decreased Stature. *Tr Am Physicians* 57: 219-26 1917.

¹²¹⁵ Bittorf Pathologie der Nebenleberkrankung in Jena 1909. *Flücker über die Pigmentbildung bei der Addison'schen Krankheit. Münchener Medizinische Wochenschrift* 70: 20-23 1923.

¹²¹⁶ Bloch H and Löffler W. Untersuchung über die Bronzefärbung der Haut bei der Addison'schen Krankheit. *Deutsches Archiv für klinische Medizin* 211: 262-91 1917.

¹²¹⁷ Szent György A. Observations on Function of Icosylase System and Chemistry of Adrenal Cortex. Description of New Carbohydrate Derivative. *Biochem J* 22: 1247-1400 1928 also On the Chemistry of the Adrenal Cortex. *Am J Physiol* 90: 536 1929.

It is well known that lemon juice which has a high vitamin C content prevents the blackening of cut surfaces of fruit e.g. avocado pears and inhibits the oxidative dopa reaction¹². Vitamin C is also able to bleach pigmentations including those of Addison's disease.

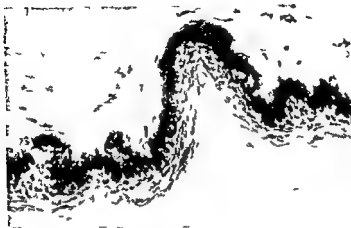


Fig. 187 — Addison's disease. (Courtesy Division of Dermatology Department of Medicine University of Chicago.)

Pigmentation of the skin and melanogen formation in the urine after exposure to light can be inhibited by previous administration of vitamin C^{12,13,14}. W. Jadassohn and Schaaf¹⁵ however showed that even large amounts of vitamin C could not prevent the pigmentation produced in guinea pigs by estrogens and other authors^{17,18} believed that the concentration of vitamin C in the human serum would not be strong enough to inactivate the dopa oxidase and to inhibit the dopa reaction as it does *in vitro*. In this connection the vitamin C deficiency in pregnancy which is a period of increased pigment formation may be mentioned.

The theory of the pigmentation inhibiting power of vitamin C would be in line with Bittorf's¹⁹ opinion that it is the higher oxidizing power and not the higher amount of melanogen which causes the Addisonian pigmentation.

Szent Györgyi²⁰ in accordance with Bloch and Löffler's^{21,22} work tried to link the theories by suggesting that vitamin C deficiency which also leads to decreased production of adrenalin might thus keep more melanogen available for production of melanin. Adrenalin is closely related to several of the melanogens (pyrrol tyrosin dopa etc.). If this double pigmentogenic role of vitamin C should be confirmed it might help to explain the high degrees of pigmentation reached in Addison's disease.

¹² J. pp. W. Kühn u. J. and Schroeder H. *Die Vitamine* Stuttgart 1935 Ferdinand Enke.

¹³ J. et al. H. A. Beitrag zur Frage des Einflusses von Vitamin C (Ascorbinsäure) auf Pigmentierungsvorgänge. *Klin. Wchnschr.* 11: 60-61 1935.

¹⁴ J. J. J. and La Croix V. Über den Einfluss der Ascorbinsäure auf die Melanogenausscheidung. *Klin. Wchnschr.* 11: 1851-1853 1935.

¹⁵ J. J. J. and Schaaf F. Über die pigmentierende Wirkung der Ascorbinsäure (Vitamin C). *Klin. Wchnschr.* 12: 845-846 1934.

¹⁶ Fantl P. and Feiler A. Vitamin C und Dopareaktion. *Klin. Wchnschr.* 24: 576-577 1935.

Hyperpigmentation has been observed in true scurvy. This observation could be used as another argument in favor of the vitamin C theory of the Addisonian pigmentation. Difficult to reconcile with the outlined role of vitamin C is the observation that this substance occurs together with melanin in the human skin.¹³⁷ Lately (Edelbacher and Zeller quoted by Robert and Zeller¹³⁸) the experimental formation of melanin from histamine by the enzyme diamine oxydase (DO) has opened a new path. In adrenalectomized animals the formation of the histamine decomposing enzyme DO is disturbed. But not more than this hint of a relationship has so far been given. A definite explanation of the pigmentation in Addison's disease has not yet been found.

Recently the role of the sympathetic system in the pigment formation in Addison's disease has again been emphasized.¹³⁹ The disturbance of the sympathetic system caused by the destruction of the adrenal cortex may lead to melanos. Hyperpigmentation due to destruction of the plexus coeliacus and other sympathetic structures by neoplasms, aneurysms or injuries is well known.¹⁴⁰ see also acanthosis nigricans nervous system

Treatment—The treatment of the pigmentation in Addison's disease has hardly been tried by other methods than those directed towards the adrenal insufficiency. Four important advances have been made during the last decade.^{139a} These are (1) the introduction of salt therapy, (2) the restriction of potassium salts, (3) the elaboration of potent extracts of the adrenal cortex and (4) the synthesis and availability of desoxycorticosterone esters. It seems as was to be expected that their value is due to the fact that they maintain life, not that they cure the destructive process in the adrenal cortex, just as insulin does not cure diabetes. In spite of the sometimes dramatic effect on most of the symptoms,^{139b} the fully developed pigmentation is hardly ever reversed. This opinion of investigators who treated many cases of Addison's disease is in contrast to other reports.^{116, 139c, 139d} Dehydration in times of remission and while under treatment with desoxycorticosterone and salt may make the patient appear lighter in color. The pigmented spots in the mouth will rarely disappear under any form of treatment.^{139e} In the rare cases of syphilitic Addison's disease complete disappearance of all symptoms including pigmentation has been seen. But unfortunately the vast majority of the cases of Addison's syndrome are due to tuberculosis.

Some metabolic parallels of adrenal insufficiency and pemphigus, especially the lowering of the chloride and protein level and the increase of the plasma volume and interstitial fluid have led to encouraging trials of desoxycorticosterone acetate

¹³⁷Coillet T. Vitamin C and pigment. *Arch Dermat Syph* **35**: 471-479 1937

¹³⁸Robert H. I. and Zeller F. A. Pigment Formation and Diamine Metabolism. *Rev of Diab Oidase Schweiz med Wchschr* **71**: 160 1607 1941

¹³⁹Von Kup T. Hautmelanone und Nebennieren. *Nichows Arch f p th Anat* **309**: 111-117 1942

^{139a}Loeb R. F. Adrenal Insufficiency. *Bull N. Y. Acad Med* **16**: 343-367 1940

^{139b}Rowntree L. G. Results of Treatment of Addison's Disease. *Med Clin N. Y. North Am* **21**: 1779-1787 1910

^{139c}Czary A. Pathogén. et étiologie des mélanodermes du type albinisme. *Trav. médi* **11**: 1921

^{139d}Loeb R. F. Adrenal Cortex Insufficiency. *J A M A* **116**: 49-50 1941

(doca) in pemphigus^{1234 1235} The recommended dose is 5 mg 3 times daily for 3 weeks and 5 mg daily thereafter Autoptic findings of severe adrenal lesions in pemphigus have been reported by Goldziher¹²³⁶

Adrenal Tumors and Hyperplasias

Adrenal cortical tumors and hyperplasia of the adrenal cortex produce a syndrome which has received several names Hirsutism¹²³⁷ which refers to the main feature of hypertrichosis is most often used Other terms are hyperadrenism genitosuprarenal syndrome and genitosuprarenal virilism The term interrenalism^{1238 1239} refers to the interrenal organ of the elasmobranch fishes which instead of adrenals have an elongated body between the kidneys closely resembling in its histology the mammalian adrenal cortex Lately the syndrome of rapidly acquired obesity of the trunk kyphosis and round shoulders striae dusky skin and hirsutism amenorrhea or impotence hypertension and fatigability has often been referred to as Cushing's syndrome¹²⁴⁰ even if it is not associated with Cushing's disease basophil adenoma of the pituitary Primary adrenal tumors of the cortex as well as of the medulla are very rare Gibson¹²⁴¹ found only one in approximately 12 000 admissions to the University of California Hospital

The adrenal cortical tumors or hyperplasias which produce the syndrome of hirsutism occur in females in 80 per cent of the cases A considerable number has been found in young children even in the newborn¹²⁴² The cortical neoplasms observed so far have been carcinomas benign adenomas sarcomas and metastatic growths from cancer of the breast or of the stomach The localization in the cortex rather than in the medulla is more important in the production of a typical syndrome than the histology of the tumor Very small adenomas may cause fully developed hirsutism No parallelism exists between the size of the neoplasm and the degree of the syndrome The hypernephromas (Crawitz's tumors) do not cause hirsutism In several instances highly malignant cortical neoplasms were found without having produced the syndrome of hirsutism¹²⁴³ (Wu quoted by Kepler and Keating¹²⁴⁴)

Dermadromes—The syndrome caused by adrenal cortical tumors is modified by sex and age In small boys precocious puberty with enlargement of the

- ¹ Talbot J H and Campbell E S Pemphigus Arch Dermat & Syph 41 3 9-36 1940
- ¹²³⁴ Collins A Ma Khem M J and Halford A J Case of Pemphigus Treated With Desoxy corticosterone Acetate J Clin Endocrinol 2 343-344 1942
- ¹²³⁵ Goldziher J W Adrenal Glands in Pemphigus Vulgaris Arch Dermat & Syph 52 4-44 1946
- ¹²³⁶ Taylor F H Hirsutism Bull et mem Soc med d Hôp de Paris 41 131 1925
- ¹²³⁷ Mathias F Hirsutism in the female on the interrenalism Zentralbl f Gynäk 50 49 1906
- ¹²³⁸ Wright A Applied Physiology 2nd ed 1940 Oxford University Press
- ¹²³⁹ Warren F I Estimation of Urinary Steroids in the Diagnosis of Adrenal Cortical Tumors Cancer Research 5 49-51 1945
- ¹²⁴⁰ Gibson T F The Diagnosis of Adrenal Tumors With Classification of Adrenal Tumor Syndromes Cases J Urol 15 3 9 1917
- ¹²⁴¹ Bayre G and Lang E J The Adrenoma Intrenall Congnita Medikologi 14 5 1934
- ¹²⁴² Hirsch E J and Keating F R Jr Diseases of the Adrenal Glands II Tumors of the Adrenal Cortex Diseases of the Adrenal Medulla and Allied Disturbances Arch Int Med 48 1010-1036 1941

penis hypertrichosis and muscular development create the type known as the infant Hercules. Even paternity has been reported.¹³⁴⁴ In adult males¹³⁴⁵ gynecomastia, feminine habitus, disappearance of the beard and a decrease in the size of the penis and testes have been observed. Less than ten cases of this particular condition have been reported.^{1345, 1346} In small girls precocious puberty, hypertrichosis, obesity and virilism are the rule while in adult females amenorrhea and virilism dominate the syndrome. Sometimes even baldness of the male type and a mustache will develop. The breasts decrease in size. This group is the largest. But it must be kept in mind that these syndromes are not pathognomonic for adrenal cortical lesions alone. Similar changes have been seen in basophilic pituitary tumors, various intracranial diseases, hyperfunctioning gonadal tumors, thymus tumor¹³⁵⁰ and other rare conditions (see chapter on puberty).

Hypertrichosis is the outstanding dermatome in cortical tumors. It is an almost obligatory, early, conspicuous and sometimes even monstrous manifestation. However, it is by no means diagnostic of adrenal cortical tumor. Not only does it occur in the above mentioned conditions, but marked degrees of hypertrichosis are frequently seen in apparently healthy women with no symptoms of any endocrine disorder. (See also chapter on Pregnancy.) Hirsutism in children with adrenal cortical tumor has been observed as early as the first year of life, even in the newborn. There are reports of young children with beards, pubic and axillary hair and heavy and pigmented lanugo growth of girls of nine with bushy eyebrows and of boys of the same age who had to have daily shaves. The pubic hair growth in these cases usually resembles the male type. The pubic change may be unilateral.¹³⁵¹ High urinary androgen output has been observed.¹³⁵²

In adult women hirsutism can produce the most unusual pictures. You should be women and yet your beards forbid me to interpret that you are so. (Macbeth I, 3.) This best characterizes the impression one gets of some fully developed cases. Some of the bearded women of the circus side shows belong to the adrenal group. The pubic hair changes to the male type. The lanugo becomes pigmented and in some parts of the body over an inch in length. Long pigmented hairs in the areolae of the nipples and coarse hair in the skin over the sternum and frequently on the mammae are conspicuous. Unusually long eyelashes have been seen.¹³⁵³ In contrast to the general hirsutism is the loss of head hair in women with adrenal cortical tumor resembling the male baldness.^{1354, 1355}

¹³⁴⁴Looney J. M. Sex Factors of the Adrenal Gland. *Endocrinology* 27: 511. 1940.

¹³⁴⁵Kepler E. F. The Adrenal Gland. Paper read before the Medical Society of Milwaukee County Nov. 21, 1939.

¹³⁴⁶Holl Cundaker. 2 männliche Fälle von N. benigne endokr. Tumoren mit funktioneller Störungen. *Deutsche Zeitschr. f. Chir.* 228: 777-79. 1930.

¹³⁴⁷Bissell G. W. and Williams R. H. Hirsutism in females. *Am. Fed. Clin. Research* (1943) 1: 35-39, 1944.

¹³⁴⁸Doonan R. J. Wilson H. M. and Heller J. L. Differential Diagnosis of Hirsutism (Cushing's) and Allied Condition (Cortical Tumors and Adrenocortical Adenomas). *Endocrinology* 27: 1-15, 1940.

¹³⁴⁹Reitner C. Ein Fall mit adrenogenitalen Genitalstörungen. *Arch. f. Gyn.* 73: 347, 1931.

¹³⁵⁰Bauer J. Lebensfunktion des gesamten N. benigne endokr. Tumoren: anatomisch und funktionell. *Klin. Wchnschr.* 42: 549-550, 1930.

Changes of the *pigmentation* in adrenal cortical tumors include occasional increased pigmentation around the nipple in adult males and in females pigmentation of the linea alba and the vulva comparable to that of pregnancy.

Unusual *acne* and comedos either in small children or in adults is almost invariably seen in cortical tumors.¹³⁵¹ The acne itself often seems to differ from the typical juvenile form and resemble the severe pyodermatic type known as *acne conglobata*.¹³⁵²



Fig 185—Adrenal cortical carcinoma. Hyperpigmentation. (Courtesy Wisconsin General Hospital.)

The amazing symptoms of *precocious puberty* in adrenal cortical tumors have led to the publication of a great number of almost identical cases. Besides the hair changes which have already been mentioned, menstruation in early childhood and breast development have often been observed. Growth of the clitoris to an erectile penis with glans coronæ and a hypospadiæ groove on the ventral surface with the labia minora shaped like a prepuce and the labia majora like a scrotum adds to the monstrosity of the syndrome. Such girls may have a deep voice. The whole body of these patients may show unusual growth with or without obesity and hirsutism. The infant Hercules, a sturdy little man with unusual muscular and intellectual development and with a large erectile penis is the rare counterpart in boys. The skin of the entire body is often mottled with dusky purplish red areas similar to *cutis marmorata*.¹³⁵³ The features in precocious puberty are bloated, the complexion dusky and congested.

Obesity is not uncommon in cases of adrenal cortical tumor, but it is more the distribution of the fat which is striking than the actual amount. The com-

¹³⁵¹Winterstein, O. The Adrenocortical Syndrome. JAMA 116:269-853, 1941.

bination of the full face, the pad in the high dorsal region and the heavy abdomen together with the thin extremities creates a characteristic habitus¹²⁴³

Next to the pituitary basophil adenoma, cortical tumor of the adrenal is the condition which is most frequently connected with *Cushing's syndrome*¹²⁴⁴

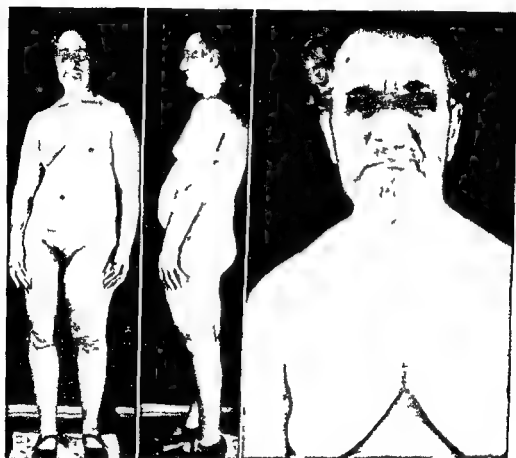


Fig. 189—Achard-Thiers syndrome (diabetes in bearded woman) (From Pullen, R. L., and Sodman, W. A., *J. Clin. Endocrinol.* Courtesy of Charles C. Thomas, Publisher, Springfield, Ill.)

Some of the cases of so-called *diabetes of the bearded women*¹²⁴⁵ belong here. In about 25 per cent of the reported cases hypertension, amenorrhea, obesity and acneiform eruptions have been noticed.^{1244, 1253}

¹²⁴³Achard, Ch., and Thiers, J., *Le virilisme phallique et son association à l'infantilisme glycolytique (diabète des femmes à barbe)*, *Bull. Acad. de Méd. Paris* 51-56, 1921.

¹²⁴⁴Shparlson, H. C., and Shapiro, F., *Diabetes of Bearded Women*, *Endocrinology* 24: 3-57, 1939.

The urinary output of androgens (17 ketosteroids) is often high in adrenal cortical tumors ¹³⁴⁴⁻¹³⁵⁴⁻¹⁸⁵⁶ There is a general tendency to interpret Cushing's syndrome with or without pituitary adenoma as caused by hyperadrenocorticalism ¹¹⁷⁻¹³⁵⁸ Striae have been seen to appear after the injection of adrenal cortical extract The diagnosis of adrenal cortical tumor is mostly suggested by the described symptoms But however striking they are all or some may be absent and in spite of their presence no adrenocortical tumor may be found The similarity of symptoms in other conditions has been mentioned The roentgenographic demonstration of cortical lesions by air injection into the perirenal fascial spaces is possible but difficult and not without danger In recent years estrogenic and androgenic substances substances which prolong survival of adrenalectomized animals and inactive substances which are chemically related to hormones have been found in the urine of patients with hyperfunctioning cortical lesions ¹¹⁹⁶⁻¹³⁴³ But these findings are no more constant than other signs and symptoms Many of the organic changes even the monstrous symptoms of feminization and masculinization are reversible if the cortical tumor is removed However since most of these neoplasms are malignant only few patients live long enough to experience the return of normalcy No confirmed dermatomes have become known in tumors of the adrenal medulla

¹³⁴⁴ Crook A C and Galloway R L The Differential Diagnosis of Basophilism (Cushing's Syndrome) by the Estimation of Urinary Androgens *Quart J Med Sci* 33: 249 1939

¹³⁴⁵ Anderson A F Hahn A M and Patterson J Adrenal Carcinoma Hormonal Diagnosis From Excretion of Pregnenolol *J Pathol & Bact* 58: 341 349 1943

¹³⁴⁶ Hirschmann H and Hirschmann P B Steroid Excretion in Case of Adrenocortical Carcinoma *J Biol Chem* 157: 601 61 1945

¹³⁴⁷ Albright F Cushing Syndrome *Harvey Lect* 28: 125 136 1943

¹³⁴⁸ Anderson E and Haymaker W Cushing Syndrome *J Nerv & Ment Dis* 99: 511 520 1944

Ho neck J Über das Auftreten und Fntteln der "Cris cutaneae" dten *Med Welt* 10: 1071 1072 1935

CHAPTER XIX

DISORDERS OF THE ENDOCRINE GLANDS

THE TESTICLES

The gonadotropic hormone of the anterior pituitary stimulates the Leydig cells in the connective tissue stroma of the testicle to produce the male sex hormone testosterone. It is excreted in the urine as androsterone which is a 17 ketosteroid. Both forms are often referred to as androgens. The international unit is the capon unit which is the biological equivalent of 100 micrograms of androsterone. Wolff¹ enumerates as functions of testosterone the development and maintenance of the accessory sexual apparatus, the growth and distribution of hair, the maturation of the skeleton, the larynx and the muscles, the distribution of fat, the control of libido and potency, and the determination of the masculine psychological pattern. The excretion of androgen which is only 1 to 15 I U per day in childhood rises at puberty to 40 to 60 I U in the male and 25 to 40 I U in the female. The reverse relationship prevails with regard to estrogenic hormone output. Beyond the age of 60 the androgens decrease¹²⁶⁵ but do not completely disappear as is the case with estrogens in old women.¹²⁶⁶

The androgens are chemically only slightly different from the estrogens, cholesterol and the bile acids (see also introduction to chapter on puberty).

Many facts demonstrating the influence of the testicle on the skin of animals are known.¹²⁶⁷ The best studied is the growth of the comb of the cock. Well known are the modifications of the plumage in male female and castrated chickens. In some species however e.g. the guinea fowl the plumage is not dependent on the gonads. The castrated male deer develops a peruke of hairy growth instead of the antlers. In the reindeer which has antlers in both sexes castration is not followed by this malformation. In the Egyptian antelope *Portia pictus* the male is gray and the female brown. The hair of the castrated male takes on the same color as the female (Zavadovsky after Sand¹²⁶⁸).

Comparable to the gonadal relations of the apocrine glands in man are the atrophy of the preputial glands in castrated mice¹²⁶⁹ and of the scent glands in the male goat.¹²⁶⁴ The improvement of the pelt in sprayed animals^{1264, 1270}

¹ Buhkr, F. Sexualhormonbefund in Harn von Männern verschiedener Alters. Ztschr. f. exper. M. 186: 6 0-654 1933

¹²⁶² Sarda, I. Die Physiologie des Hols. In: Hirsch, H. H. d. innere Sekretion vol. Leipzig 1933 Curt habilitat.

¹²⁶³ Gom, H. F. Die Präputialdrüsen des Mannes in ihrer Abhängigkeit vom Hormon des Hoden. Ztschr. f. Hirsch, H. H. d. innere Sekretion 1933: 1 1933

¹²⁶⁴ Hirsch, H. Die Hautdrüsenorgane (Harnschweiß, Drüsen, Inguinaldrüsen, Präputialdrüsen, Analdrüsen, Hautdrüsen, etc.) in der Laboratoriumsuntersuchung und der Praxis ihrer Abhängigkeit von den Geschlechtshormonen. Ztschr. f. Zellforschung u. mikr. Anat. 18: 217-233 1933

¹²⁶⁵ Hatakeyama, A. Studien über die castation bei den Tieren. Compt. rend. Soc. de biol. 126: 633 1933

¹²⁶⁶ Hirsch, H. F. Die Bedeutung der Kastration bei der Entwicklung der Hoden. Ztschr. f. Zellforschung u. mikr. Anat. 18: 217-233 1933

¹²⁶⁷ Olsson, A. V. Der Einfluss der Hyperandrogenisation nach Verneff auf die Produktion der Wolle und die Entwicklung der Körperform. In: Schaffner, Trudi. Genet. Inst. ex. per. v. t. 8: 51-79 1933

seems to be in contradiction with the favorable effect on the fur following the administration of testosterone or transplantation of testicular tissue in Jenik dogs.¹³⁶⁷ Castration and testosterone treatment demonstrated the gonadal dependence of the striking fur characteristics of the male baboon.¹³⁶⁸ The pig ment formation in man is also stimulated by testosterone (Milro after O Henslein 41)

The reduction of the readiness for anaphylaxis by removal of the testis and the restoration of a normal capacity for allergization by hormonal substitution has been demonstrated by Yun (after E Urbach). The number of mitoses in the epidermis and hair follicles of the male white mouse decreases substantially after castration.¹³⁶⁹

Much evidence has been accumulated suggesting a stimulating effect of androgens on number, size and function of the sebaceous glands, oil glands and thickness of the epidermis,¹³⁷⁰⁻¹³⁷¹ and an increase of the production of prepuccial "megra".¹³⁷ Acne hirsutism, obesity, husky voice and enlargement of the clitoris has been observed in women who have been treated with testosterone propionate because of menstrual disturbances.¹³⁷² Folliculitis of the nose and of other parts of the skin and acne occur sometimes in men who receive androgenic therapy.

Eunuchism and Eunuchoidism

Eunuchism is the syndrome resulting from loss of the testes while eunuchoidism characterizes the state of gonadal deficiency in the male.*

Early Castration—Loss of the testicles before puberty causes prolonged patency of the epiphyseal clefts with resulting excessive length of the extremities and fingers. The voice does not change, the muscles fail to gain the masculine strength and no libido develops.

Dermadromes—Most striking is the failure to develop the sexual characteristics. The penis remains small and may be retracted into the scrotal skin which is thick and not unlike the labia majora. The body hair is scanty and the beard is absent with the exception of a little "mug" on the upper lip. In later age a scanty and bristly "old woman's beard" appears on the chin and around the angles of the mouth. If there is a development of pubic hair it is of the female type. The hair line along the forehead does not develop, the temporofrontal

*The terms eunuchism and eunuchoidism should be reserved for gonadal deficiencies in the male.
¹³⁶⁷Zahl H. R. Juvenation of "Cull" Dog by Means of Testicular Preparations and Their Effect on Testicles and Prostate. *Virchows Arch. Path. Anat.* 305: 65-107, 1939.

¹³⁶⁸Zuckerman H. and Parkes A. C. Secondary Sexual Character in Monkeys (Castration). *J. Endocrinol.* 1: 430-49, 1939.

¹³⁶⁹Ortiz-Pedra J. M. On the Effect of Castration on the Proliferative Activity of the Epidermis and of the Hair Follicles. *Rept. Biol.* 2: 43-46, 1933. *Zbl.* 48: 11.

¹³⁷⁰Hooke C. W. and Pfeiffer C. A. Growth Effects of Sex Hormones. *Lipo. Body Growth Skl.* H. I. and 4. Sebaceous Glands in Rats. *Endocrinology* 32: 69-76, 1943.

¹³⁷¹Rony H. R. and Zakon G. J. Effect of Androgen on the Sebaceous Glands of Human Skin. *Arch. Dermat. & Syph.* 48: 601-604, 1943.

¹³⁷²Hamilton J. H. Male Hormone Substitution. *Prim. Factor. J. Clin. Endocrinol.* 1: 570-592, 1941.

¹³⁷³Greenhill T. H. and Freed J. C. Villin in Women Caused by Androgenic Therapy for Menstrual Disturbances. *J. A. M. A.* 112: 1573-1574, 1939.

Late Castration—If the loss of the testicles occurs after puberty the changes are less pronounced and even libido and potency may remain to some degree. The observations on such cases are plentiful. Hot flashes are felt by some castrates shortly after the loss of the testicles but they do not become as distressing a symptom as sometimes occurs in the female climacteric. There is a tendency towards loss of body hair¹²⁷⁸ which usually takes on a female distribution¹²⁷⁹. A patient of Lissner¹²⁸⁰ who shaved four times weekly before the loss of his testicles had to shave only once a week afterwards. In some adult castrates the beard remained unaffected^{1280, 1278}.

The yellow component of the castrate's skin is caused by carotene which is present in excessive quantity.¹³⁸⁰ Pallor pigmentation and carotene content can be influenced by testosterone administration. The panniculus adiposus is often increased with concentration on the thighs, the hips and the abdomen. Weight gains of twenty five pounds are common and the basal metabolism is usually lowered.¹³⁷⁹ Some eunuchs however are lean. Gynecomastia is common¹³⁸¹ but the breasts consist of fat only and not of glandular tissue.¹³⁷⁴

- ¹³⁷ Löwenthal K Der Eneuchoidismus des Mannes Beitr z path Anat u z slig Path ■
 426-439 1931
^{137a} Scheuer O F Die Behaarung d Mensch u Leipzig 1933 Curt I abitz ch
^{137b} Tandler S and Gross J Die Skopzen Einfluss der Kastration auf den Organismus Arch
 Entwicklungsmech d Organ 30 2 235-253 1910
^{137c} Marsano ■ Manual de las enfermedades endocras y del m tabolismo Libreria Hach tt
 Buenos Aires 1933
^{137d} Rackfield A W Leber die Kastration bei 40 s uell Abnorm n Monatschr f Psychiat u
 Neurol 87 1-31 1933
^{137e} McCullagh E F and Renshaw J F Effects of Castration in Adult Male J A M 4 103
 1140-1143 1934
^{137f} Edwards P A Hamilton J B Dunley S A and Hubert G Cutaneous Vascular at
 Pigmentary Changes in Castrate Men Endocrinology 28 119 1 s 1941
^{137g} Koch W Die russisch armenische Kastratenakte der Skopzen Veröffentl a d K lgs m
 konstitutionspath 2 1-33 1921
^{137h} Pottard E La castration chez l'homme Rech res sur les adeptes d'un ecte d'uques
 mystiques les Skoptzy Arch suls d anthrop gën 8 213 235 1973
¹³⁷ⁱ Lange J Die Folg n der Entmannung (an Hand der Kriegserfahrungen dargest llt) Leipzig
 Georg Thieme 1934

The face often has a sleepy expression. This is caused by a small fat pad in the upper eyelids which narrows the space between the lids. Slight puffiness of the face is an early and common symptom after adult castration¹³³². The face often becomes finely wrinkled in a peculiar shriveled or papyraceous way which does not correspond to the normal facial folds.

Increase of the thickness of the nails in an adult castrate which could be reversed by testicular substance was seen by Lissner¹³³⁴ although nail changes were missed in the twelve cases of McCullagh and Renshaw¹³³⁵.



Fig 190 — Eunuchoid in a young man aged 18 years. Beard axillary chest pubic hair absent. Frontotemporal hair line without masculine notch.

All or some of the features of eunuchism may be seen in the syndrome of eunuchoidism which is not rare as the experiences in the military induction centers have shown. Heredity is a factor in this constitutional endocrine anomaly^{1374 1375}.

The *male climacteric* is an objective reality¹³³⁶ and not mainly a matter of neurasthenia and hypochondry¹³³⁷. However no definite dermatomes which

¹³³²Lissner H. Onychauxis in an Eunuchoid. Remarkable Improvement by Implantations of Testicular Substance. Arch. Dermat. & Syph. 10: 150-157. 1924.

¹³³⁴Carmichael H. T. and Kenyon A. T. Eunuchoidism. Arch. Neurol. & Psychiat. 40: 717-742. 1934.

¹³³⁶Hellreth G. and Myers G. B. The Male Climacteric. J. A. M. A. 126: 472. 1944.

¹³³⁷Blum A. Das Problem des männlichen Klimakteriums. Wien klin. Wchnschr. 49: 1133-1139. 1936.

are linked to the physiological decline of the testicular function have become known. The keratoderma palmarum et plantarum climactericum described by Huthausen in the female has also been reported in ageing men¹³³⁸. In a recent analysis of 54 cases of the male climacteric¹³³⁹ itching hot flashes and sweating occurred in about one third of the instances. Androgenic therapy seems to be promising.

Common Baldness

Since the common type of baldness occurs almost exclusively in men it is natural to think of causes peculiar to the male sex. R. O. Stein¹³⁴⁰ who first described the calvities frontalis (see puberty) which is largely characteristic of the male hairline and is usually lacking in eunuchoids and women has suggested that the common baldness of males is a continuation of the physiological frontal baldness. Seborrhea and tension of the scalp with impaired circulation are contributing factors. Several authors^{1341, 1342} suggest that baldness of the common type is a generalized primate trait which occurs in a similar pattern in apes and monkeys. Heredity is a definite factor^{1343, 1344}. In 1932 Sabouraud¹³⁴⁵ quoting the famous observation of Aristotle that neither the child nor the woman nor the castrate become bald added that we know hardly more on the subject. The situation does not seem to have changed. However we have learned that administration of male hormone to eunuchoids and castrates can produce baldness of the common type. Premature alopecia of the male type has also been seen in virile women with arrhenoblastoma or supranatal virilism. It ceases to progress when the abnormal masculinization ends¹³⁴⁶.

Unfortunately endocrinology has not yet shown a practical way to prevent or cure baldness. Castration prevents baldness but this surgical approach has so far not been suggested in seriousness though it has been hinted.

Gynecomastia

Gynecomastia may occur in an otherwise normal puberty. Ten cases were recorded per 100 000 personnel in the United States Navy¹³⁴⁷. The type occurring in otherwise normal young men is more often unilateral than bilateral¹³⁴⁸. It is also occasionally seen in the male climacteric¹³⁴⁹. It is often pronounced in Fröhlich's syndrome and in eunuchoidism. In rare instances it is associated with a variety of neoplasms which have retained the endocrine functions of the

¹³³⁸Henschen G. Palmar and Plantar Keratoderma. Schweiz med. Wchnschr. 70: 690-691 1940

¹³³⁹Stein R. A. A. Male Climacteric. 54 Cases. J. A. M. A. 127: 70, 710 1945

¹³⁴⁰Stein R. O. Über die Entstehung des Haarausfalls aus dem endokrinen System und über die Mögl. heil. einer endokrinen Therapie d. Glatze. Wchnschr. 49: 449-450 1930

¹³⁴¹Miller O. S. Jr. Human Hair and Primate Fatterness. Smithsonian Misc. Collect. 33: 10 1931

¹³⁴²Ratten R. H. Ordinary Baldness. Arch. Dermat. & Syph. 46: 201-213 1941

¹³⁴³Osborn D. Inheritance of Baldness. J. Hered. 7: 347 1916

¹³⁴⁴Hamilton J. B. Male Hormone stimulation is prerequisite and sufficient in Chimpanzee Baldness. J. Invest. Dermat. 6: 473-4 1947

¹³⁴⁵Sabouraud G. V. Gynecomastia in the Navy. M.D. Gerson 35: 375-379 1944

¹³⁴⁶Jennville J. H. Gynecomastia. Hys. 15: 157-159 1937

¹³⁴⁷Richardson T. G. Gynecomastia. Lancet 1943: 1: 304-30

soil from which they originated. Such tumors include^{1398 1399} instances of adrenal cortical tumor^{1344 1400} eosinophil adenoma of the anterior pituitary pinealeoma neoplasms of the midbrain or of the hypothalamus and thymic tumors. The best known endocrine neoplastic cause however are tumors of the testicle especially teratomas and the rare chorionepitheliomas with high estrogen production^{1401 1402}

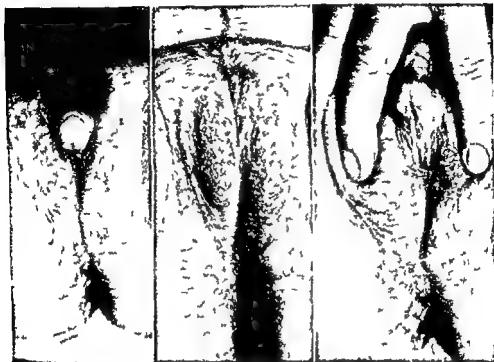


Fig 101

Fig 102

Fig 103

Figs 101 102 103—Lusitich maphroditism. Female aged 19 yrs. Ovaries infantile uterus vagina 10 cm length female distribution of pubic hair but erectile phallus of 4 cm scrotal apperance of labia majora male body configuration husky voice vigorous beard growth like a girl. (Court of Wisconsin General Hospital)

¹³⁹⁸Wells F I. Gynecomastia—Enloe and Tam. *Am J Pres* 212 155-157 1914

¹³⁹⁹Klaus B. Über Gynäkomastie. In *Beitrag zur Kenntnis der Beziehungen zwischen Keimdrüsen und Geschlechtscharakteren*. Arch Gynäk 141 503-535 1930

¹⁴⁰⁰Geschlekt C F. Supra-renal Tumors. *Am J Cancer* 23 104-174 1935

¹⁴⁰¹Storjensen H H. Ein Fall von Chorionepitheliom im Hoden mit Gynäkomastie. *Fra kftu t Ztsch f Path* 42 80-95 1932

¹⁴⁰²Jordan H W. Gynäkomastie bei einem Kranken mit malignem Testiculotom. *Ned rltijdschr v g neesk* 77 2915-79 3 1933 2:1 48 149

¹⁴⁰³Zondek B. Malign Hodentumoren und Hypophysealdrüsen. *Homo al Diagnostik au Horn Hydrocele nistweitg H und Tumoren der Klin Wehrsch II* 74 270 1932

¹⁴⁰⁴Gordon W B. Pathology of 142 Cases of Primary Neoplasm. In *Man J Urol* 43 72-733 1940

¹⁴⁰⁵Lewin M L. Gynecomastia. *J Clin Endocrinol* 2 511-514 1941

¹⁴⁰⁶Bonn H K and Evans N. Chorionepithelioma in Male and Gynecomastia. *Am J Surg* 88 125-132 1942

This symptom has furthermore been seen to follow prostatectomy and the administration of cholesterol¹⁴⁰⁷ adrenal cortical extract¹⁴⁰⁸ and desoxycorticosterone (Doca)¹⁴⁰⁹. It is a frequent finding in cirrhosis of the liver (see chapter on diseases of the liver). Failure of the cirrhotic liver to destroy estrogens may be the cause of gynecomastia in severe hepatic disease¹⁴¹⁰ (Zondek B. after Edmondson).

Testosterone has been shown to cause complete regression or reduction of the hypertrophy of the male breast in 26 out of 28 cases¹⁴¹¹. Surgery has been recommended¹⁴¹².



Fig. 194.—Same patient as shown in Figs. 191-193. (Courtesy Wisconsin General Hospital.)

Hermaphroditism

The presence of testicles does not necessarily produce male sexual characteristics. Female hair and other sex characteristics have been found together with microscopically verified testicles¹⁴¹³. In 1 case of hermaphroditismus veru

¹⁴⁰⁷Dunn C. W.: Stilbestrol—(Estrog.)—Induced Gynecomastia in Male. *J. A. M. A.* **113**: 2073-2084, 1940.

¹⁴⁰⁸Bronstein T. E.: Gynecomastia. *Endocrinology* **21**: 274-277, 1939.

¹⁴⁰⁹Lawrence R. D.: Gynecomastia Induced by Desoxycorticosterone Acetate (Adrenal Extraction). *Brit. M. J.* **1**: 137, 1943.

¹⁴¹⁰Glass S. J., Edmondson H. T. and Roll R. N.: Hormone Changes Associated With Liver Disease (Gynecomastia in Cirrhosis). *Endocrinology* **27**: 49-75, 1940.

¹⁴¹¹Hoffman W. J.: Gynecomastia. Hormone Therapy. *Am. J. Cancer* **58**: 17-251, 1939.

¹⁴¹²Welsman A. T. and Schwartz A.: Intersexuality. *J. A. M. A.* **117**: 249-251, 1941.

lateralis^{1 98} with a testicle in the right side of the scrotum and an ovary and uterus in the left side of the scrotum, breasts pubic hair and other characteristics were of female character¹⁴³ They changed to the male after the removal of the ovary and uterus

Tumors of the Testicles

Except for the symptoms of precocious puberty and gynecomastia which may be caused by tumors of the interstitial tissue of the testicles no skin manifestations seem to be known in tumors of the testicles

^{14 3}Lattimer T H Engl E T and Yeaw R C True Hermaphroditism J L of 80 481-488 1913

CHAPTER XX

DISORDERS OF THE ENDOCRINE GLANDS

THE OVARIES

Our knowledge of the influence of the ovaries on the skin in animals is much greater than that of the comparable facts in man. In the capon it is possible to produce a female plumage by injections of folliculines¹⁴⁴. The feathers of an adult capon are so sensitive to injections of estrogens and placenta extracts that the failure to inject the hormones one day a week in a series of daily injections is recorded by a black bar in the breast feathers in their regeneration after being plucked¹⁴⁵. This pigmentary reaction can be used as a pregnancy test¹⁴⁶ utilizing urine which can be read in 48 hours. In the oophorectomized Leghorn chicken the injection of small doses of theelin in olive oil causes a change in the regenerating feathers from male type back to female so that alternating bands of female and male color can be obtained¹⁴⁷. While the time for the regrowth of the hair after shaving is the same in both sexes in immature rabbits it is shorter in the mature female longer in the mature female castrate and shorter again in males feminized by estronization¹⁴⁸. Infiltration of the capon skin with estrogen locally inhibits the characteristic feather changes seen in castrates¹⁴⁹. Continued subcutaneous injections of estradiol benzoate produces shagginess and marked loss of hair in the rat. The estrogen treated rat has a thinner dermis and epidermis and the sebaceous glands are reduced in size and number. All these changes can be prevented by administration of androgen¹⁵⁰.

The implantation of ovaries into the kidneys of castrated male guinea pigs produces intense pigmentation of the nipples unless these are situated in albinotic skin¹⁵¹.

¹ Carlirolto E. De l'action du hœmat de follicule sur le plumage du coq domestique. *Compt rend 90 de Biol* 118 523 6 1913

² Juhr M. ■ Armour F. F. and Gustavson R. G. Plumar and Oviduct Response to Female Hormon in Fowls. *Endocrinology* 16 349 354 1930

³ Craswell A. W. and Blyth J. G. G. *Diagnosis of Fowl Pregnancy from Egg* 90c London 4 B 16 247 257 1934

⁴ Mitchell J. B. Jr. Action of Theelin on the Domestic Fowl from Egg. *Exp r Biol & Med* 30 300 1933

⁵ Hu C. K. and Frazer C. N. Effect of Ovary and of Urinary Estrogen on Growth of Hair in Rabbit. *Anat Rec* 77 155 161 1910

⁶ Quinn J. P. and Burrows W. H. Effects of Female Sex Hormone on Plumar Color. *J Hered* 26 290 303 1935

⁷ Greenwood and Blyth. Variation in Plumar Response of Brown Leghorn Capon to Female. *Proc Roy Soc London s B* 119 97 132 1935

⁸ Frud J. On the Biological Tests of the Female Sexual Hormone. Menformon Influence on Feathers. *Rec ges Phycol* 67 371 1932

⁹ Bloch H. and Schraff A. Experimentelle Untersuchungen über den Einfluss des Ovarial Hormons auf die Färbung. *Arch f D mat u Syph* 165 264 283 1912

Ovarian Insufficiency

In *aplasia* of the ovaries the pubic and axillary hair is sparse or lacking. The rest of the hair has in some cases been seen to be underdeveloped.^{14,15}

In B. Bloch's^{14,15} case juvenile cataract and poikiloderma were present.

Primary ovarian insufficiency may lead to a habitus with overlong extremities and also to dwarfism.^{1319,14,15} The syndrome of primary ovarian insufficiency is characterized by excessive amounts of urinary follicle stimulating hormone and low levels of 17 ketosteroids. There is lack of breast and uterine development and other symptoms of infantilism. The axillary and pubic hair is scanty but not absent. Albright and his coworkers believe that the growth of the axillary and pubic hair in females is not stimulated by the ovary but by an adrenal cortical hormone (see chapter on Puberty). Melanoderma and mild depressive psychosis in ovarian deficiency have been described by S. Block^{14,17} and later by Bonilla^{14,18} and Marañon (after Bonilla^{14,19}).

Naturally a great amount of information is available on the female *castrate*. The cutaneous symptoms after castration of the adult female are essentially those of the menopause. However it should be emphasized that castration of the woman does not always change her appearance.

Secondary ovarian hypofunction clinically characterized by amenorrhea or irregularity of the rhythm and amount of the menstrual flow usually does not cause dermatomes though hypertrichosis is frequently encountered.^{11,9,14,21} The hypertrichosis may disappear with the restoration of a normal ovarian function. It seems that hypertrichosis in ovarian hypofunction is due to the relative weakness of the prohibiting effect of the estrogen. Such an imbalance may be caused by ovarian deficiency as well as by adrenal cortical hyperfunction. The urinary excretion of 17 ketosteroids has in many instances of hypertrichosis been found above the normal level.^{14,2,14,22} Application of estradiol salve and intra dermal injections of progynon are able to make the local hair growth disappear^{14,23} but the effect cannot be relied upon. The administration of stilbestrol in primary

¹² Bloch B. Poikiloderma atrophicum mit Mangel der Ovarien. Endokrinophle. Juvenile Katarakt u. Lebere r ghs k l t d Parasympathicus. Schweiz med. Wchnschr. 88: 753-756 1926.

¹³ Olivet J. Ueber den angeborenen Mangel beider Eierstöcke. Kastration und Differenzierung. Frankfurt Ztschr. f. Path. 29: 477-491 1933.

¹⁴ Goljwasser J. Ein Fall von Aplasia ovariorum mit plurifolliculärer Dysfunktion und mit durch Transplantation von Ovarium behobener Amenorrhoe. Arch. f. Gynäk. 183: 166 1933.

¹⁵ Larn J. F. K. 300 A. T. and Loch F. C. Ovarian Dwarfism. J. Clin. Endocrinol. 2: 137-145 1942.

¹⁶ Block S. A. New Syndrome. M. Red. 90: 994 1916.

¹⁷ Bonilla E. Insuffisance ovarienne mélangée à troubles psychiques. Rev. franç. d'endocrinol. 1: 3: 404-45 1955.

¹⁸ Solomon W. Th. Hypertrichosis bei Frauen. Arch. f. Frauenk. 13: 155 1927.

¹⁹ Lasser H. Feminization and Dimasculinization of a 17-Year-Old Girl by Injection of Stilbestrol. F. docriology 27: 355 1940.

²⁰ Strassmann F. O. The doctrine of Testosterone of Masculinization. Growth Associated With Masculinization in Women. J. Internat. Coll. Surgeons 4: 137-141 1941.

²¹ Hambli E. C. Cuyler W. K. and Baptist M. Uterine Excretion of 17 Ketosteroids in Ovarian Failure in Hirsutism and Virilizing Syndromes. J. Clin. Endocrinol. 2: 763-77 1941.

²² Gree R. Androgen and Pregnenolone Excretion in Hypertrichosis. Lancet 2: 486-487 1940.

²³ Munster-Journier J. C. and Albrieux A. Absorption of Sex Hormones by Skin. Case of Facial Hypertrichosis Improved by Intradermal Injections of Progynon. Presse méd. 48: 409-50 1940.

amenorrhea is often followed by hyperpigmentation of the linea alba and nipples¹⁴³. This was not observed in the stilbestrol treatment of menopausal complaints.

Ovarian Tumors

Cysts and teratomas rarely cause dermatomes except those connected with hypoovarism. Granulosa cell tumors in children may cause precocious puberty¹⁴⁴ but there do not seem to be skin manifestations in adult patients.

—5—



FIG. 193. Precocious puberty. Female aged 6 years. Removal of ovarian tumor at age of 7 years. Immature development started at 3. Characteristic of a child. Bone age 13½ years. (Courtesy Wisconsin General Hospital.)

¹⁴³Dayl M E, Hayton M W, Johnson J H & Koshmar M. Stilbestrol in the treatment of Endocr. Origin. J. Endocrinology 8: 138, 1950.

¹⁴⁴Meyer R. Some Species of Ovarian Tumors and Their Relations to the Characteristic Am J Obst & Gynec 22: 89-117, 1931.

*Dysgerminoma*¹⁴³⁶ or seminoma ovarii is rare. This type of neoplasm has been observed in pseudohermaphroditic individuals. The external genitalia are infantile. These tumors which usually occur in the second and third decades do not masculinize the patient.¹⁴³⁶

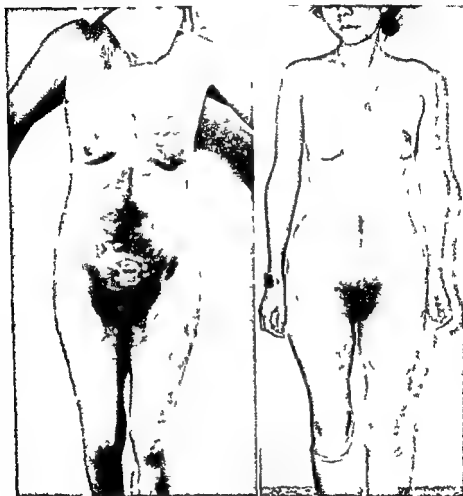


Fig. 100. Mawell ligand tumor before and after operation. (From Blaumenfeld, J. Obst. & Gynec.)

Irrhenoblastomas cause defeminization and masculinization. Baldness of the masculine type may develop; characteristic deposits of fat may vanish; the breasts, the other ovary, and the uterus may atrophy, and amenorrhea may ensue. There is enlargement of the clitoris, atrophy of the labia majora, and marked hirsutism of the male type with beard growth. The symptoms are reversible by successful operation. The tumors arise from the seminiferous tubules in the hilus ovarii or from a primitive ovotestis. The histologic picture

shows adenomatous structures resembling seminal tubules and/or epithelial cords. The endocrine testicular function accounts for the deep biological changes.¹⁴⁴¹

In *Carcinoma*¹⁴⁴¹ *Luteoma*^{1443 1445} *Sarcoma*¹⁴⁴⁶ and *Hypernephroma*¹⁴⁴⁷ masculinizing features have been described in rare instances. Kepler¹⁴⁴³ observed



Fig. 197—Female aged 20 years. Facial hypertrichosis in ovarian tumor of unknown pathology.

Cushing's syndrome in a case of adrenal like tumor of the ovary. There was excessive excretion of 17 ketosteroids but a normal urinary output of estrogens. In rare instances¹⁴⁴⁸ diffuse erythematous edema of the skin has been observed as a peculiar form of metastases from ovarian carcinoma (see chapter neoplasms).

¹⁴⁴¹McIntyre W. H. Arrhenoblastoma. *J. Obst. & Gynec. Brit. Emp.* 49: 41-50, 1942.

¹⁴⁴²Edell F. Geschlechtsumstimmung durch Ovarialtumor (Arrhenoblastoma). *Arch. f. Gynäk.* 149: 3-36, 1933.

¹⁴⁴³Mathias E. Operativ entfernte Arrhenoblastom mit späterer Schwangerschaft. *Zbl. f. Gyn.* 87: 449-455, 1933.

¹⁴⁴⁴Norris F. H. Arrhenoblastoma. *Am. J. Cancer* 32: 1-39, 1934.

¹⁴⁴⁵Lee R. H., Salme A. and Morton H. H. Arrhenoblastoma. Removal followed by feminization and pregnancy. *Obstet. & Gynec.* 1: 769-781, 1942.

¹⁴⁴⁶Esau J. Histologisch Gesichtsbildung. *Klin. Wchnsch.* 8: 160, 1971, III, J.

¹⁴⁴⁷Blackmun R. L. Tumor With Masculinizing Syndrome. *Am. J. Obst. & Gynec.* 43: 1036, 1941.

¹⁴⁴⁸Cosacenco A., Drageaescu G., Georgescu M. and Dinulescu H. T. Luteinizing hormone contribution anatomically. *Etud. du virilisme ovarien. Pres. Acad.* 29: 1-61, 1971.

¹⁴⁴⁹Mayer J. Maccully J. Luteoma. *How Arch. f. path. Anat.* 309: 6-613, 1942.

¹⁴⁵⁰Colberg. Mischgeschwulst des Ovarium (knorpelhaltiges Sarkom) männliche Haarung, Stimulierung und Histiohypertrophie. *Zbl. f. Path.* 52: 1162-1164, 1929.

¹⁴⁵¹Trolldenier A. Histologisch. *Wie Ovarialtumor. Histolog. f. Path. u. d. Geschwulst. Anat.* D. 11: 1115, 1970, 711, 23, 460.

¹⁴⁵²Ulrich F., Waldow J. and Stamm C. J. Diffuse Cutaneous M. tactile Lesion From an Ovarian Carcinoma. *Arch. Dermat. & Syph.* 25: 96, 1970.

Small blue *Angiomas Papillomas* and *Fibromas* in large numbers may occasionally accompany tumors of the female sexual organs¹⁴⁹ Such benign growths of the skin are seen in the menopause as well as in pregnancy and abdominal diseases

Ovarian Relationship of Dermatoses—In the light races women are supposed to be more often brunette than men¹⁵⁰ New investigations seem necessary The preponderance of the female sex in some dermatoses is well known Examples are hemangioma lupus erythematosus lupus vulgaris and some other types of skin tuberculosis scleroderma Raynaud's disease chloasma acrodermatitis atrophica some circumscribed keratoses¹⁵¹ urticaria pityria rosea eczema impetigo herpetiformis erythrocyanois cruris erythema nodosum Paget's disease of the nipple tinea versicolor^{152 153 *}

In order to accept the ovarian etiology in a given dermatosis the claimed relationship should be supported by menstrual or menopausal coincidence disappearance in pregnancy cure by hormonal therapy cure by castration after failure of other therapy and by other evidence of gonadal character The literature of the last fifty years abounds with such reports^{154 155} However no dermatosis has been described which by its morphological picture alone would invariably permit the diagnosis of an ovarian dysfunction or disease

Cases of Purpura^{156 157} psoriasis^{158 159} keratoderma palmare and plantare^{160 161} erythema perstans¹⁶² rosacea urticaria and angioneurotic edema

Men are more subject to the following dermatoses lichen folliculosum lichen planus dermatophytosis inguinalis Kaposi's hemodermic pigmentary sarcoma and of the lower lip and mouth and sinusitis

¹⁵¹ Freund H W Hautbrosche a g r n u g nitalkrank n Frau Arch f Dermat u Syph 47 410 1894

¹⁵² Haevelok Ellis Mann und W H Würzburg 1900 Cutis habitus ch

¹⁵³ Noak J Beiträge zwischen Haut und weiblich m G nital Bl logi und Path logi des Weibes vol 3 B klin III 7 Urban & Schwarzenberg

¹⁵⁴ Alle J The Relationship of Sex to Disease Ann Int Med 7 1000-1012 1934

¹⁵⁵ Scheue O Hautkrankheit m s uell n Ursprungs bei Frauen B ln 1911 Urban & Schwarzenberg

¹⁵⁶ Fahl Menstruelle Hausters h i ung Dermat Wchnsch 54 531 191

¹⁵⁷ Wenne I Die Beziehungen der G nitalorgane zu Hautveränderungen Hall a 9 19 4 Carl Wirthold

¹⁵⁸ C s lle C A Rob purpura n srica Rev ud am de enlo rincol 21 76 794 1934

¹⁵⁹ Urbach E Fok in bedingt jah z hatela g bestehe de Purpura a Zbl 42 164 163 1933

¹⁶⁰ Meid G M I be konstitution il m n tru lie rheumatoide Purpura Tolla ha mat 38 418-421 19 2

¹⁶¹ Vogt F Psycho und Ovarialfunktion Monatschr f furtch u Gynäk 81 24 39 19 9

¹⁶² Linton G Psoriasis Arthropathy in Women Whose Ovaries Have Been Removed Operatively Joliff J o c z p at 45 1606 1610 1935

¹⁶³ B r o-Miera A Qu di u caso di keratoderma simm tri a palmar plant in d a am orroica guarita on p parati opot rapici Riv d ost t ginec prat III 1 1930 Zbl 24 4 9

¹⁶⁴ Kai T and Shibata S Keratodermitis palmari proger edra A ta i rm tol japo III 653 654 19 9

¹⁶⁵ Matsui I and Fajngold A Erythema perstans und das enlokri Gy t m Odeas med J 2 607 19 4 Zbl III 0

(see menopause)^{1464 1465} alopecia areata^{1466 1467} eczema^{1467 1471} prurigo dermatitis herpetiformis¹⁴⁷ parapsoriasis^{14 3} pruritus¹⁴⁷⁴ and many other dermatoses have thus been linked to ovarian dysfunction. Bohnstedt¹⁴⁷⁵ found the urinary excretion of pituitary gonadotropic hormone increased in rosacea and dermatitis dysmenorrhea symmetrica. Chloasma in nonpregnant women and other pigmentations are in some cases of ovarian origin¹⁴⁷⁶. They have occasionally been cured by local application of strong estrogen salve¹⁴⁷⁷.

¹⁴⁶⁴ Sáinz de Aja M A. Urticaria pigmentosa akutes Quinckesches Oedem und Neurodermitis geheilt d. Thyroid- u. Ovariumtherapie. Actas dermo sif 22 473-474 1930 Zbl 36 77

¹⁴⁶⁵ Blach M. Durch endokrine Störungen bedingte Urticaria. Deutsche med. Wchnschr 85 184 195 1930

¹⁴⁶⁶ Řihová V. Alopecia areata und Ovarialstörungen. Česká dermat. Šamberger Festschr pp 530 534 1931 Zbl 34 43

¹⁴⁶⁷ Garnier G. Eczema Due to Estrogen Lutein Disequilibrium 2 Cases. Bull. Soc. franç. de dermat. et syph 46 319 327 1939

¹⁴⁶⁸ Desaux A. À propos de la communication de M. Georges Garnier sur l'eczéma par le déséquilibre hormonal folliculo-lutéinique. Bull. Soc. franç. de dermat. et syph 46 627-630 1939

¹⁴⁶⁹ Berger M. Dermatologische Beziehungen einzelner Frauenkrankheiten endokrine: Ursprungs. Schweiz. med. Wchnschr 65 36 367 1935

¹⁴⁷⁰ Urbach H. Endokrin bedingte Haut- Schleimhaut- und Haarerkrankungen. Arch. f. Dermat. u. Syph 161 492 503 1930

¹⁴⁷¹ Szego P. Ekzem mit Ovarialstörungen. Gyógyászati 68 306 1929 Zbl 27 788

¹⁴⁷² Riecke E. Dermatitis herpetiformis. Handb. d. H. u. Gk 7 2 612 1931

¹⁴⁷³ Cartia B. Un caso di parapsoriasis lichenoides condismenorrea guarito con la cura opoterapica. Glo. Ital. di dermat. e sif 69 1423 1437 1928

¹⁴⁷⁴ Leszczyński R. von and Ijebba E. Hormonale Frauendermatosen. I. Ueber lichte präklimakterische und klimakterische Hautreaktionen. Dermat. Wchnschr 88 1289 130 1931

¹⁴⁷⁵ Bohnstedt R. M. Untersuchungen über Ausscheidung von Prolactin und Follikulin im Harn von Hautkranken. Klin. Wchnschr 88 1675 167 1934

¹⁴⁷⁶ Schörlke K. H. Chloasma uterinum in nonpregnant women. Med. Welt 13 1413 1414 1939

¹⁴⁷⁷ Rocca F. Estrogenic Substances in Treatment of Chloasma. J. Clin. Endocrinol 2 217 1934

CHAPTER XXI

PUBERTY

Puberty is the transition from childhood to adult age seen mainly from the viewpoint of sexual maturing. In the female sexual maturing means the establishment of regular menstruation. In the male emission of semen must be considered the beginning of sexual maturity but this event is much less sharply accentuated and usually forgotten in adult life. Around the beginning of the production of mature gametes is grouped the development of the *secondary sex characters*. Furthermore puberty is a period of intensified organic growth and reorganization which affects almost every part of the body. Finally it is a period of psychic and intellectual ripening and adjustment. The onset of menstruation is but little speeded up by such factors as race and warmer climate probably more by urban life better living conditions and psychological factors.¹⁴⁷³ In the United States the menarche starts between twelve and fifteen years most frequently at 13.9 (Engelmann after Novak¹⁴⁷⁴) compared with 15.5 in the corresponding zone in Europe.

Dermadromes of Puberty—The establishment of the cycle follows within a year, the growth of the pubic and axillary hair. The subcutaneous fat padding gradually smoothens and rounds the skeletal and muscular contours. Typical fat accumulations are found in girls on the cheeks shoulders breasts buttocks lower abdomen mons veneris and thighs.¹⁴⁷⁵ Girls develop less pigment than boys. Neurath¹⁴⁷⁶ considers little bunches of veins in the skin of the thighs to be a female sex characteristic. In boys a palpable sometimes tender subareolar node of mammary gland tissue often appears at the onset of puberty and disappears at the end. Temporary gynecomastia in boys is seen occasionally.¹⁴⁷⁷

The *apocrine glands* start their secretion at puberty earlier in girls than in boys. The glands represent a type of skin gland which is in close relationship to the gonads. The apocrine glands are sweat glands which develop from the hair follicles and open into the hair follicles which the ordinary sweat glands the so-called small or eccrine glands never do. They do not secrete sweat but give off a secretion consisting of particles of the secreting cell protoplasm. Thus their type of secretion places them between the sebaceous and the sweat glands many authors consider the apocrine glands to be a rudiment of the scent glands of many mammals. Such glands are known to have a close relationship to the sexual life. The peculiar odor of the human axilla which is different from the

¹⁴⁷³Novak F. Menstruation and Its Disorders New York 1931 H. Appleton & Co.

¹⁴⁷⁴Neurath H. Physiology and Pathology of Puberty in von Pfaunder Schlossmann The Diseases of Children vol I Philadelphia 1935 J. B. Lippincott Co. pp 501-526.

¹⁴⁷⁵Junk E. T. and Shafton A. L. Mastitis Mastoplasia Mastalgia And Gynecomastia in Normal Adolescent Males Illinois M. J. 73 115-123 1939.

The prepuberty male castrates develop slightly less pubic and axillary hair than normal females. Oophorectomized females do not lose their body hair however it falls out in Simmonds disease Addison's disease myxedema and very old age. In all these conditions the excretion of 17 ketosteroids is very low.¹³¹⁸ The axillary hair also disappears in hepatic cirrhosis (see cirrhosis).



Fig 105 — Male distribution sternal patch of hair. No other endocrinal abnormalities.

Girls of course are supposed to have a smooth skin without noticeable hair except in the pubes and in the armpits. But quite often considerable hair growth along the legs, arms, on the upper lip and even in the sternal region of the chest can be seen without any detectable endocrine abnormalities. This tendency is more pronounced in some pigmented races e.g. the mediterranean.^{1319, 1320} A peculiar accumulation of long pigmented hairs is not infrequently found around the female nipples although it is rarely seen in men.

During adolescence the *hairline* which is the border of the scalp hair acquires its characteristic configuration. The fairly straight frontotemporal hairline of children develops in boys a more or less marked triangular hairless notch which points in the direction of the vertex where the male baldness will develop later. According to R. O. Stein¹³²¹ who described this as the *calvities frontalis adolescentium* it is not observed in castrates nor in eunuchoids nor in women except in masculinizing conditions. This rule has not too many exceptions. The *calvities frontotemporalis* is seen in the vast majority of the men and in only less than 6 per cent of the women (Maranon after Mussio Fournier¹³).

While the male hair in front of the ears unnoticeably merges into the beard, sideburns are seen only in women who have other symptoms of hirsutism. Maranon (after Mussio Fournier¹³) sees a sexual difference in the hairlines of the nape of the neck. In the female the borderline is distinct and shows two lateral prolongations and sometimes a medial one consisting of strong hairs. In the

¹³¹⁸Friedenthal H. Das Haar kleid des Menschen. Jena 1905.

¹³²⁰at in R. O. Fournier's *Revue de Dermatologie* 1905.

male the transition from the head hair into the lanugo of the nape of the neck is more gradual. This characteristic is not very pronounced. The male eyebrows are thicker, longer and less regularly implanted. They have a greater

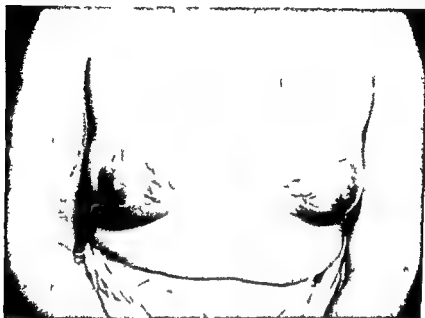


Fig. 100 —Hypertrichosis of brows. The patient is of age 30. He has a strong facial hair growth and a decidedly masculine hairline. No definite endocrine disturbance could be found. The 17-ketosteroid excretion was normal. 

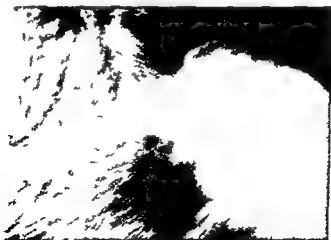


Fig. 101 —Female aged 30 years. Callosities temporales in the same patient as shown in Fig. 100.

tendency to grow together on the glabella. The development of the eyebrows in the male parallels the general hairiness. In middle age some very long hairs appear in the eyebrows. In some men the eyebrows take on a bushy appearance.

which is never observed in women. The *evelashes* are stronger, longer and more curved in women than in men.

Shaving usually becomes necessary between the ages of sixteen and seventeen. At first, the rate of beard growth is very slow, requiring shaving only once a month or less. Marañón (after Mussio Fournier¹²) distinguishes a period of juvenile beard growth on the lateral upper lip, zygomatic chin and submaxillary regions from the mature beard which forms by coalescence of the growth centers.

The color of the hair often deepens during puberty, particularly from sixteen to nineteen. This may be due to increased oiliness or to increased pigmentation (Breipohl after Jung^{14,15}). The latter is true if there is a hereditary factor of pigmentation which had not yet become manifest. Blond Jewish children often darken considerably in this age.

Certain strands of elastic fibers in the skin of the face which have been described under the name of *elastica mimica* develop at puberty and degenerate



Fig. 901. Striae not related to pregnancy, ascribed to loss of weight. (Courtsey Division of Dermatology, Department of Medicine, University of Chicago.)

slowly after the age of forty.¹⁶ *Striae distensae* occur frequently in both sexes during adolescence. They are common in the skin of the lower back, across the thighs, above the patellae, and on the upper arms. They usually run transversely to the length of the body or of the limbs in symmetrical, rarely unilateral arrangement. In the lower back they are typically found in parallel lines below

¹² Jung, F. T. The Eby 1001 El Chaga In Infant to Puberty Illinois 51 J 80 477-494 1941

^{14,15} Vohwi kel, A. H. Leber di Alt rs nach E u g n den Hautbindeg w bes und über di sog u ante Elastica mimica bei verschied n n Rassen D mat Ztschr 62 95-104 1931

the twelfth dorsal vertebra sometimes occupying almost the whole width of the back down to the center of the sacral area. Their¹⁴⁹ appearance often coincides with growing pains in the limbs. The distribution of the striae in puberty suggests a mechanical factor. But it is likely that a toxin which weakens the elastic fibers plays a part. Some authors consider the appearance of striae in infectious diseases an ominous sign but there is little foundation for this belief. (See striae in chapter on pregnancy.)

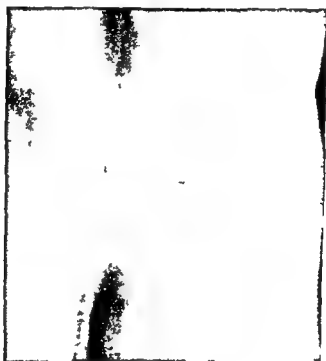


Fig. 702 — Male aged 12 years. Striae of a 101 sec.

True *precocious puberty* is the phenomenon of early sexual maturity apparently not due to endocrine or cerebral disease but to unknown constitutional possibly hereditary factors. This constitutional type without endocrine tumor occurs in girls and is probably the most frequent variety of precocious sexual development.¹⁴⁹ The advanced development in these cases sometimes starts during intrauterine life. Menstruation without accompanying gross endocrine disease is known to occur several years before the normal time of onset.

All the sequences of puberty are hastened including the changes in skin and hair. The dermatologic aspect of early maturity is discussed in the chapter dealing with adrenal cortical tumors which are frequently responsible.

¹⁴⁹ Peigès H. *Verges d' Croissance ou des adolescent*. Nouv. H. Igatigu. Dermat. et G. vol. VI Paris 1936. Masson & Co. p. 55.

¹⁴⁹ Nowak F. The Constitutional Type of Female Precocious Puberty. *Cases*. Am. J. Obst. & Gynec. 47: 70-41 1944.

Almost identical syndromes of precocious puberty can be caused by anterior pituitary hyperfunction by pinealomas¹⁴⁹² and other cerebral conditions of heterogeneous etiology¹⁴⁹⁴. The latter include tumors (glioma) of the corpora mammillaria hypothalamus¹⁴⁹⁵ and other regions brain abscesses tuberous sclerosis¹⁴⁹⁶ and encephalitis lethargica¹⁴⁹⁷. Precocity is also a part of Albright's syndrome (see there). It furthermore occurs in some conditions of the ovaries such as hyperovarianism¹⁴⁹⁸ ovarian cysts¹⁴⁹⁹ arrhenoblastoma teratoma¹⁴⁹⁹ and granulosa cell tumors. Precocious puberty is a characteristic of hyperorchism caused by neoplasms arising from the endocrinal (interstitial) part of the testis.

Delayed puberty is seen in connection with hypopituitarism hypogonadism and hypothyroidism. In gonadal deficiency the thymus is usually persistent¹⁵⁰⁰.

Skin Diseases of Puberty

Acne vulgaris is surely the most important and common dermatosis of the puberty age. Pollitzer¹⁵⁰¹ in 1914 gave its incidence in the United States as 7.5 per cent of all dermatoses but it seems even more common today. There is hardly a boy or girl who is not at some time and in some degree afflicted with it. It is almost a physiological disease.

Follicular keratosis comedo formation and seborrhea are the primary lesions of acne. Inflammation of acute or chronic character with or without abscesses and finally healing with a scar is the sequence of secondary symptoms. The face back and the sternal region are most commonly involved. The microscopic examination of early lesions shows a follicular keratosis and epithelial atrophy accompanied by loss of the finer elastic fibrils near the epithelial wall¹⁵⁰². This latter fact may account for the open pores.

Gonads Age Sex—The most obvious relations exist with the gonads. Acne is extremely rare in early childhood although it has been seen before the age of one year especially in males^{1503 1504}. From five to eleven years the incidence curve rises slowly without severe cases. Then it soars distinctly coinciding with the appearance of pubic and axillary hair the development of the breasts

¹⁴⁹²Björk J. F. Globus J. H. and Simon H. Pubertas Praecox. Pinealoma. J. Mt. Sinai Hosp. 4: 935, 1934.

¹⁴⁹³Caarella P. La puberté précoce nelle cerebropatie infantili. Rass. gen. di studi psichiat. 24: 855-896, 1935.

¹⁴⁹⁴Weinberger L. M. and Grant F. C. Precocious Puberty and Tumors of the Hypothalamus. Arch. Int. Med. 67: 87, 1941.

¹⁴⁹⁵Cornil L. and Kie J. P. Macrogonitismo précoce. Attrib. à une tumeur du lobe antérieur de l'hypophyse. Reu. neurol. 1: 86-89, 1930.

¹⁴⁹⁶Ford E. R. and Cullis H. Precocious Puberty Following Males Fungal Pharyngitis and Epidemic Encephalitis. Relation of Intracranial Tumors and Inflammatory Process to the Syndrome of Macrogonitismo Praecox. Bull. John Hopkins Hosp. 60: 19-33, 1937.

¹⁴⁹⁷Z. d. L. dau M. Fall von vorzeitiger Geschlechtsreife. Nervenheilk. 15: 510, 1933.

¹⁴⁹⁸Grund H. Pubertas praecox als Folge chorion epithelium. Wochenschr. 1933.

¹⁴⁹⁹Pollitzer S. Acne Vulgaris. J. Cutan. Dis. 32: 312, 1914.

¹⁵⁰⁰lyn E. F. W. Acne Vulgaris. Histologi. Changes in Early Lesions. Arch. Dermat. & Syph. 59: 1940.

¹⁵⁰¹Ja. n. J. J. Infantile Acne Vulgaris. J. Pediat. 20: 365-367, 1915.

¹⁵⁰²Gray A. M. H. Acne in a Child Aged 7 Years. Proc. Roy. Soc. Med. 27: 9, 1934.

¹⁵⁰³Aitken R. Acne in Infants. Brit. J. Derm. 54: 273, 1911.

and the onset of the menses¹⁵⁰⁵ Girls develop acne earlier in life : At the age of seventeen almost every boy or girl has some though often inconspicuous blackheads or pimples : The severe cases are seen in girls from fourteen to sixteen in boys between sixteen and nineteen¹⁵⁰⁶ Boys have a little higher morbidity and show severe cases more often : This has been shown in investigations of many thousands of adolescents in various countries^{1505 1507}

Some statistics give a lower incidence but it seems that they only take into account the more severely inflammatory cases : After the age of twenty acne becomes less and less frequent but there is no sharp upper age limit : Even in the fourth decade acne is not uncommon in men and exacerbations in women at the onset of and even after the menopause occur : There does not seem to be acne vulgaris in the aged

Next to the coincidence of acne with the onset of puberty the time relationship to menstruation suggests a gonadal factor : It is common knowledge and it has often been confirmed by medical observation that acne exacerbates before during or after the menses the individual case usually remaining constant to type with regard to the time relation of the exacerbation¹⁵⁰⁸ The intermenstrual remission is often complete : However similar menstrual flare ups can be seen in lupus erythematosus psoriasis rosacea eczema^{1505 1509} and other chronic dermatoses Therefore the menstrual exacerbation itself is a weak argument for the gonadal cause more so since it occurs in only a certain percentage which varies from about 30 to 75 per cent in several observed series of girls : Menstrual disorders and hypogonadism are no more frequent in girls with acne than in those without acne^{1501 1506 1510 1511}

A great deal of work with modern methods has been done in order to find better proof of an imbalance of hormones in juvenile acne than is furnished by statistical and clinical methods : This work showed that in patients with acne the output of estrogen in the urine is below the normal level : Rosenthal and Kurzrok¹⁵¹² and later Rosenthal and Neustaedter¹⁵¹³ were unable to find any estrin in twenty seven out of thirty four young women with acne : These low urinary estrogen contents in patients with acne were confirmed by a number of authors

In men with acne the excretion of estrogen was also found to be well below normal : On the other hand the output of androgen in men was found to be higher in acne patients while it was found in normal level in women : Only Cornbleet and Barnes¹⁵¹⁴ found the daily urinary androgen output in male and female

¹⁵⁰⁵Hoch H : Zur Pathogenese der Acne vulgaris Zbl 44 510

¹⁵⁰⁶Hurrichs W J and Ivy A C : Incidence in Chicago Region of Acne Vulgaris Arch Dermat & Syph 37 975 987 1938

¹⁵⁰⁷Q hwa tzman J : Abnormalities (Adolescence) J Pediat 21 93 10 1941

¹⁵⁰⁸Urtach F and Schiller W : Der heutige Stand des Akneproblems Akne sexualit. Med Klin 33 1 01 1703 1937

¹⁵⁰⁹Cohn E L : Incidence of Clinica Acn in Men La cet 1 169 191

¹⁵¹⁰Rach I b r die B i hung n d r Acn zu Allg meinerk a kung DL B r n 1907

¹⁵¹¹Cunningham R L and Lun for I C J : Acne Related Cause California & West Med 33 28 29 1931

¹⁵¹²Rosenthal T and Kurzrok R : F etion of Estri in Acne Proc Soc Exper Biol & Med 30 1150-1151 1933

¹⁵¹³Rosenthal T and Neustaedter T : Estrogenic Substance in the Blood of Patients With Acne Arch Dermat & Syph 32 560-567 1933

¹⁵¹⁴Cornbleet T and Barnes B : The Hormones and Acne Vulgaris Arch Dermat & Syph 40 249 25 1939

patients with acne a low normal ¹⁵¹ Wile¹⁵¹ and his collaborators impressed by the relatively high and unchanging androgen findings believe that the ratio between urinary androgen and estrogen is of great significance. They found its value in acne much higher about double of the normal figures. These observations have essentially been confirmed ^{151a 1517}

The excretion of sex hormones in the pre acne age of less than eight is very small and the same for both hormones in both sexes. From eight to eleven both steroid sex hormones rise the androgen quicker in the male the estrogen quicker in the female. When adulthood is achieved the normal characteristic ratio of the excreted sex hormones is established ¹⁵¹⁸. Acne is characteristic for the years of transition when the ratio is changing just as it is characteristic for the catamenia. At this point of the menstrual cycle the urinary output of estrogens has reached its lowest level ^{1519 1520}. The androgens excreted by the woman do not fluctuate with the cycle so that a relative preponderance of androgens exists at and around menstrual time when acne is well known to exacerbate. There is much evidence that male eunuchoids do not have spontaneous seborrhea and acne ¹⁵²¹ but may acquire it during treatment with androgenic preparations just as women and also men often do under treatment with testosterone propionate ¹⁵²². It is noteworthy that acne produced in eunuchoids by injection of testosterone propionate disappeared on withdrawal and reappeared on resumption of the injections ¹⁵. Boys generally have an increasing incidence of acne from seventeen to twenty one years and their cases are often more severe with a greater tendency to pyogenic infection and involvement of the trunk ¹⁵⁰¹. It is a general impression that virile boys are more likely to show acne than those of a more feminine type ^{1 98} and also that girls with severe acne are of less marked femininity. The occurrence of acne in masculinizing tumors of the adrenals the pituitary and the ovaries has often been observed. Zimmer¹⁵²³ found gynecomastia more often together with acne than with normal skin but his series is small.

Long before it was possible to prove any changes in the level of sex hormones the attempt had been made to cure acne with organ extracts which in the light of our present knowledge probably had very little potency. Later a great number of investigations were made with preparations of undoubted potency. Anterior pituitary like gonadotropic hormone prepared from urine of pregnant women has been tried by scores of authors. While most of them found little or no

¹⁵¹ Wile U I Know J M and Bradbury J T. Sex Hormones in Acne Arch Dermat & Syph 39 200-10 1939

^{151a} Lawrence C H and Wertheissen N T. Endocrin Dyscrasia of Acne in Women Endocrinology 27 735-748 1940

Lawrence C H and Wertheissen N T. Acne in Females Internat Clin 1 199 05 1942

¹⁵¹⁷ Nathanson J T Town L E and Aub J E. Sex Hormones in Urine and Acne Endocrinology 25 851 1941

¹⁵¹⁸ Smith O V and Smith O W. Urinary Excretion of Estrogens and Gonadotropic Hormones During Menstrual Cycles Period of Conception and Early Pregnancy N W England J Med 215 908 1936

¹⁵¹⁹ Diemann E and Laque E. Ned i tidskrift v skensk 84 3 47 1940

¹⁵²⁰ Calkins H Salmon L J Cairnes J A and Walt R R. Biological Effect of Androgen (Testosterone Propionate) in Women JAMA 114 1339 1544 1940

¹⁵²¹ Hamilton J H. Treatment of Acne in Eunuchoidism with Synthetic Male Hormone Substanc Endocrinology 11 619-624 1933

¹⁵²² Zimmer E. Gynecomastia and Acne vulgaris Diss. Friburg 1935

value some claimed benefit^{15 1}. Just as variable were the results with estrogens but it seems that good results outweigh the poor results though not very impressively. II Zondek^{15 2} showed that follicular hormones can produce estrus



Fig. 203. 1b. Familial tendency to acne. Father and son. Mother and daughter.

phenomena if applied percutaneously. This has since been shown in many experiments. The practical application of this observation in the treatment of acne by ointments containing estrogens and androgens has mostly been disappointing.

¹ Lawrence C. H.: The Anterior Pituitary Hormone. A Clinical Study of Its Effect in Acne Vulgaris. J. A. M. A. 100: 943-947, 1936.

² Zondek H.: Local Treatment of Acne With Follicular Hormones. Schweiz. med. Wochenschr. 65: 1164-1169, 1935.

Luteal hormones have been recommended but have had little trial compared with estrogens. The alternating use of large doses of estrogens during the first ten days following the menses and luteal hormone on five consecutive days during the third week of the cycle was followed by lasting improvement in five girls after three months of treatment (Urbach and Schiller¹⁵⁰³). Considering the fluctuating course of acne a sceptical attitude toward all reports of small numbers of cases is justified. Androgens have been tried in the treatment of acne in spite of the many experiences with their acneogenic effects. The reports are overwhelmingly discouraging. In several experimental series¹⁵¹⁴⁻¹⁵¹⁶ controls received injections of bland sesame oil. The effects were about just as good as with androgen in sesame oil—and both were not too poor. In summarizing the gonadal relationship of acne one is permitted to say that the age incidence, menstrual accentuation, occurrence in masculinizing tumors, nonoccurrence in male eunuchoids, urinary and blood content of sex hormones and the production of acne with androgen injections proves its existence. However the degree of our knowledge of the mechanisms involved has not yet yielded a reliable method of hormonal therapy. This opinion is reflected in a symposium on acne of leading American dermatologists. Not one out of five dermatologists used hormonal therapy to a larger extent than as an adjuvant.¹⁵¹⁷

Hypertrichosis in girls with or without other signs of endocrine disturbance usually causes a great deal of anxiety. The patients or more often the parents soon become worried about the possibility of serious pituitary or adrenal disease. After investigation this question is fortunately most often answered in the negative. But then the cosmetic problem remains. It is beyond the scope of this book to deal with the treatment of hypertrichosis. But it may be mentioned that endocrine therapy so far has only been successful if other endocrine symptoms especially amenorrhea were present.

The outbreak at puberty of *chronic dermatoses* like *psoriasis*, *lupus erythematosus* and *epidermolysis bullosa* has been observed sufficiently often to make coincidence unlikely.¹⁵¹⁸ In Recklinghausen's neurofibromatosis the number of tumors existing from early childhood may suddenly increase so that the fully developed syndrome results. Onset of lipoma formation in puberty has become known in Dercum's disease. It seems correct that in adolescence the tendency to keloid formation is more marked than before. A keritosis involving the volar surfaces of the fingers of Japanese girls and mostly starting after the first menstruation has been described by Dohi and Miyake under the name of *keratoderma tylodes palmaris progressiva*. Takesita¹⁵¹⁹ reported 217 cases seen in ten years and Kawabe¹⁵²⁰ 50 cases.¹⁵²⁰ Dysmenorrhea and increased basal metabolism have frequently been observed. It seems that besides gonadal factors

¹⁵⁰³ Urbach H. M. Treatment of Acne Vulgaris With Testosterone Propionate. *Endocrinology* 22: 503, 1934.

¹⁵¹⁷ Symposium on Practical Management of Acne Vulgaris. *J. Invest. Dermat.* 2: 143-17, 1946.

¹⁵¹⁹ Takesita H. Keratoderma tylodes palmaris progressiva. *Hitsu to Hitsu* 5: 93, 1937, 211.

¹⁵²⁰ Kawabe M. Diagenant. Keratoderma tylodes palmaris progressiva. *Jap. J. Dermat. & Syph.* 31: 11, 1933.

¹⁵²¹ Kitamura S. Keratoderma tylodes palmaris progressiva (Dohi and Miyake). *J. J. Dermat. & Syph.* 29: 9, 1910, 1929. *Zbl. H.* 164.

occupational causes play a part. The condition has rarely been seen in boys. The *favorable* influence of puberty is noticeable in certain dermatoses. This is true of urticaria pigmentosa and of infantile eczema. Only a small percentage of cases of infantile eczema are carried over into adult age in the form known as atopic dermatitis. Such a stubborn and resistant disease as tinea of the scalp, particularly microsporia, has a marked tendency to heal spontaneously at puberty although there are exceptions to this rule. The fact that tinea of the scalp usually heals at puberty may be due to the higher acidity during puberty. The pH of the infantile skin drops from 6.2 — 6.4 to 4.5 — 5.6.¹⁸¹

¹⁸¹Dancroft J. R. Hormones and Skin. California & West Med 61: 60 1944

CHAPTER XXII

MENSTRUATION

The Menstrual Cycle^{1182 1229 1531}

The anterior pituitary by means of prolactin A a protein like hormone activates the ovary. The follicle stimulating fraction of the prepituitary hormone causes the maturing of the graafian follicle during the first half of the menstrual cycle the luteinizing fraction prolactin B after the ovulation on the fourteenth day makes the corpus luteum grow in the empty follicle.

During the entire cycle the follicle secretes the steroid estrogens. The estrogen blood level reaches its peak immediately before the onset of the menses and drops to its lowest point during menstruation. There is another peak at the time of ovulation at midterm. The estrogens cause the proliferative changes in the uterine mucosa during the first two thirds of the cycle. The corpus luteum produces another steroid hormone progesterone which reaches its high in the circulation during the last third of the intermenstruum. It causes the premenstrual secretory changes of the uterine mucosa which are preparatory for the embedding of the ovum. If there is no fertilized ovum forthcoming the uterine mucosa breaks up and menstruation results. The corpus luteum wanes.

More than fifty years ago when menstruation was still believed to be a reflex von Ott¹¹⁸² the first to speak of a menstrual cycle traced over a full month the pulse temperature blood pressure caloric loss muscular power capacity of the lungs and other physiological functions. He found that all these manifestations of vitality increased slowly in intensity during the whole intermenstruum to reach a maximum immediately before the onset of the menstrual flow. Then a steep decline during menstruation brings the levels back to the starting point. Since these studies many investigations have been made along the same lines. They mostly revealed parallel cyclic changes of vitality and reactivity. Many of the cyclic phenomena can be linked with cutaneous changes.

Blood—The number of erythrocytes decreases slightly during the intermenstrual period. During menstruation it first rises then falls and rises again after menstruation (Polzl after Novak¹⁴⁷⁹). The hemoglobin fluctuation is slight. There is a moderate leukocytosis during the first day of menstruation.

The thrombocytes reach a maximum at the time of ovulation and a minimum during menstruation. Catel and Schotola¹⁵³¹ traced the decrease of the thrombocytes to the influence of the corpus luteum hormone and suggested the use of the reaction of the thrombocytes as a test for the potency of corpus luteum

¹¹⁸²Frank R T. Puberty Menstruation Pregnancy Bull. New York Acad Med 11 83 97 1940

¹²²⁹von Ott H. Des lois de la périodicité de la fonction physiologique dans l'organisme féminin Arch. d'obst. et de gynéc 5 507-508 1890

¹⁵³¹Catel J W and Schotola H. Thrombocyte Variation and Corpus-luteum Hormone Med. Klin 24 973 976 1940

preparations The tourniquet test is often positive before¹⁵²⁶ and during menstruation^{1526 1547 1550} The prothrombin level is probably lowered and the coagulation time lengthened shortly before the onset of menstruation With menstruation rise of the prothrombin and return of the coagulation time to normal or even higher than normal takes place

The blood sugar shows a premenstrual rise¹⁵⁴⁰ The carbohydrate tolerance is lowered in menstruating diabetic women and acidosis and coma may be precipitated The more frequent occurrence of acidosis in women below forty five years of age than in males of this age may be linked to the influence of the menstrual hyperglycemia^{1541 1544}

High blood cholesterol has, in some cases been seen to return to normal during menstruation¹⁵⁴³ It seems that the blood cholesterol falls during or near menstruation and is followed by a rise above normal level^{1544 1545}

There is a tendency to premenstrual water retention One third of forty two women showed weight increase before and during the catamenia In some cases edema is noticeable^{1546 1548} especially about the lower legs and ankles The urticarial (lymphagogue) reaction to intracutaneous injections of minimal doses of morphine is stronger in the premenstrual period while the vasoconstrictive action of adrenalin is weaker at the same time¹⁵⁴⁹

The general hydration is probably accompanied by increased succulence of the skin which explains the menstrually increased firmness of the hair implantation in the skin¹⁵⁵⁰ On the last premenstrual day it takes more than double the weight necessary to pull a hair out than at the end of the period

¹⁵²⁶ Bickel L I am da Endothelsymptom als Test für Diagnose und Therapie ovarialer Funktionstörung angegeben werden? Deutsch med Wchschr 67 1103 1108 1931

¹⁵⁴⁰ Deglmann T Akute Entzündungskrankheiten und Prämenstruum München med Wchschr 25 Jg 1910

¹⁵⁴¹ Adams W Die Prothrombinspiegel im Zyklus der geschlechtsreifen Frau Zbl f Gynäk 66 103 106 1942

¹⁵⁴² Weisling F Prothrombin Level and Coagulation Time of Sexually Mature Women Ztschr f exp r Med 113 374 1943

¹⁵⁴³ Hull J Die Capillarreaktion und ihre Beziehung zur Menstruation bei der Frau klin Wchschr 20 260-68 1941

¹⁵⁴⁴ Mo H C and Her mann F Sugar Metabolism and Insulin Therapy in Acute Vulgaris Brit J Dermat 51 477 1953 52 13 129 1940

¹⁵⁴⁵ Cammer H J The Influence of Menstruation on Carbohydrate Tolerance Canad M A J 47 51 1942

¹⁵⁴⁶ Kahl R H Einfluss der Menstruation auf den Blutzuckergehalt Wien klin Wchschr 107 918 1914

¹⁵⁴⁷ Hill R F Cholesterol in the Vaginal Epithelium Ztschr f 137 1914

¹⁵⁴⁸ Okuy R A and Levy A C Study of the Metabolism of Women Epithelial Content of Blood and Metabolism J Biol Chem 22 261 1927

¹⁵⁴⁹ Welford A and Morrison J Natural Resistance and Clinical Medicine Boston 1911 Little Brown & Co

¹⁵⁵⁰ Welford J A Menstrual Fertility Preliminary Report J A M A 102 31 1931

¹⁵⁵¹ Atkin A and Levy A C Metabolism of Women Epithelial Content of Blood and Metabolism J A M A 106 515 517 1936

¹⁵⁵² Mo H C and Ruben I Mit der Menstruation zusammenhängende Dermatologische Genese Klin Wchschr 53 369 37 1931

¹⁵⁵³ Kroll A and Levy A C Abhängigkeit der Haarwurzelentwicklung von der Haut bei Frauen in Abhängigkeit vom menstruellen Zyklus Correlation of the Hair Root Development with the Menstrual Cycle J A M A 102 31 1931 32 31 1932 33 31 1933

In the intermenstruum the resistance against pull rises to a medium figure. Newer investigations have in part failed to confirm these claims.¹⁵⁴¹

Menstrual swelling of the liver was already observed by Chvostek.¹⁵⁵ Menstrual icterus has been the subject of several investigations.¹⁵⁶³

Von Leszcynski¹⁵⁵⁴ found that in eighty seven out of one hundred menstruating women whom he tested with intracutaneous injections of 0.02 per cent trypan blue the disappearance of the deposit was faster than normal. This test seems to demonstrate an increased activity of the reticulo endothelial system.

The sensitivity of the skin to ultraviolet light in the premenstrual phase is often higher than normal. The return to normal sensitivity to light occurs during menstruation beginning on the first day.^{1555 1556} This may be correlated with the simultaneous fluctuations of the blood calcium, potassium and iron¹⁵⁵⁵ and especially of the estrogens. In this connection the observations of Hamilton¹⁵⁵⁹ concerning the significance of the sex hormones in the tanning of the skin of women may be mentioned. In women who were either in the spontaneous menopause or castrated, marked tanning occurred only after injection of estrone or testosterone propionate. Then the pigmentation appeared in areas which as long as two months previously had been exposed to light while areas protected by the shoulder straps and the bathing suit did not tan. Thus the steroid sex hormones acted like a photographic developer.

Spontaneous allergic reactions like asthma¹⁵⁶⁰ as well as those elicited by tests are often stronger immediately before or during the catamenia. The sites of old positive intradermal reactions may flare up again during menstruation.¹⁵⁶¹ Patch tests are sometimes negative when done in the intermenstruum and positive when repeated during menstruation (Tzanck and Sidi after Urbach¹⁵⁷⁰). Urbach¹⁵⁷⁰ advises not to increase the dose for pollen desensitization during the menses because of the possibility of acute reactions. The Dick test for scarlet fever is sometimes temporarily falsely positive during menstruation. On the other hand a negative Dick test during menstruation is to be considered highly reliable. Some observers¹⁵⁶² found the highest reactivity to various allergens on the last

¹⁵⁴¹Whitaker W. L. Hair Root Strength and Menstrual Cycle. J. Invest. Dermat. 6: 305-307 1945.

¹⁵⁵Chvostek. Die menstruelle Leberhyperämie. Wie klin. Wchnschr. 9: 93-207 1909.

¹⁵⁵⁴Leszcynski. Menstruelle Gelebsucht. Beil. klin. Wchnschr. 9: 615-618 1872.

¹⁵⁵⁵Leszcynski. R. on the influence of the female genital organs on the reticulo-endothelial system of the skin. Monat. Wehnschr. 161: 1109-1117 1933.

¹⁵⁵⁶Guthrie. The effect of sex hormones on the skin. Ultraviolet light sensitivity and menstruation. Cyclu. Strahlentherapie 48: 4-9 1933.

¹⁵⁵⁷Dick. The effect of the menstrual cycle on the skin. Einfluss von Menstruationszyklus und Schwangerschaft. Strahlentherapie 27: 54-59 1917.

¹⁵⁵⁸Ellis. The effect of the menstrual cycle on the skin. Einfluss von Menstruationszyklus und Schwangerschaft. Strahlentherapie 44: 1-10 1931.

¹⁵⁵⁹Hamilton. The effect of the menstrual cycle on the skin. Einfluss von Menstruationszyklus und Schwangerschaft. Strahlentherapie 48: 182-191 1933.

¹⁵⁶⁰Hamilton. The effect of the menstrual cycle on the skin. Einfluss von Menstruationszyklus und Schwangerschaft. Strahlentherapie 48: 182-191 1933.

¹⁵⁶¹Hamilton. The effect of the menstrual cycle on the skin. Einfluss von Menstruationszyklus und Schwangerschaft. Strahlentherapie 48: 182-191 1933.

¹⁵⁶²Guthrie. The effect of the menstrual cycle on the skin. Einfluss von Menstruationszyklus und Schwangerschaft. Strahlentherapie 48: 182-191 1933.

¹⁵⁶³Hamilton. The effect of the menstrual cycle on the skin. Einfluss von Menstruationszyklus und Schwangerschaft. Strahlentherapie 48: 182-191 1933.

¹⁵⁶⁴Hamilton. The effect of the menstrual cycle on the skin. Einfluss von Menstruationszyklus und Schwangerschaft. Strahlentherapie 48: 182-191 1933.

day of menstruation the next strongest in the midperiod and the lowest on the premenstrual day. Thus the greatest reactivity of the skin would coincide with the period of estrogenic deprivation. The sensitivity to tuberculin has been found greatly reduced during menstruation.¹⁵⁶³

There seems to be little or no influence of menstruation on the results of serologic tests for syphilis.¹⁵⁶⁴

Menotoxin—Popular belief has always held that a menstruating woman exerts a poisonous influence on her environment. Dough kneaded by a menstruating woman would fail to rise and fruit canned in this condition would not keep. In 1878 the British Medical Journal discussed the question whether the

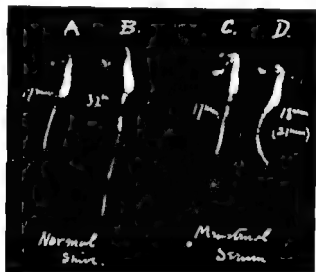


Fig. 201.—Toxic influence of menstrual serum on the growth of seedlings of lupinus albus. A, length of roots at the start. B, root after 24 hours in shive solution. C, D, after 24 hours in 1 per cent menstrual serum in shive solution. The root has increased only 4 mm instead of 15 mm. Menstrual serum inhibits the growth of lupinus but much less. (From Macht, D. J., *J. Pharmacol. & Exper. Therap.*)

general belief was true that if a woman cured hams while menstruating the hams would spoil. Similar beliefs are found in almost all countries.¹⁵⁶⁵ The question whether cut flowers wither quicker if handled by a menstruating woman was first studied seriously by Schick,¹⁵⁶⁶ who from his experiments believed that the blood and sweat of menstruating women exert a poisonous influence on cut flowers and yeast. He found a marked difference in the life time of cut flowers held over varying periods of time in the bare hands of menstruating women compared with that of flowers handled by the same person wearing rubber gloves or in the intermenstrual period. Dough kneaded by a menstruating person rose to only half the volume of the control.

¹⁵⁶³Letters to W. E. and Miles C. Relation of Menstruation to the Fermentability of the Skin Capillaries and the Autonomic Tonus of the Skin Vessels. *Arch. Int. Med.* 38: 730-735, 1936.

¹⁵⁶⁴Jingraham N. R. and Mayer V. H. Menstrual Cycle and the Blood Serologic Test for Syphilis. *Am. J. Syph. Gonorr. & Ven. Dis.* 21: 23-24, 1940.

¹⁵⁶⁵Geigel H. Die Menstruation gift. *Wien klin. Wochenschr.* 23: 39, 1910.

On the suggestion of von Gröer Schick¹⁵⁶⁵ called the hypothetic poison menotoxin Saenger¹⁵⁶⁶ in insufficiently reported experiments was unable to confirm Schick's¹⁵⁶⁵ claim of a menotoxin. He experimented mainly with mice which after the injection of menstrual blood failed to show toxic symptoms. The most interesting part of Schick's¹⁵⁶⁵ experiments which were in accordance with the popular belief was the toxicity of menstrual blood and sweat to plants. Macht¹⁵⁶⁷ who had developed a much more sensitive and quantitative phyto-pharmacological test method confirmed the existence of a menotoxin with well planned and controlled experiments. He together with Lubin¹⁵⁶⁷ used the length of roots and stems of growing lupinus seedlings and the cultural growth of yeast as indicators. They found a toxic substance present in the serum blood cells saliva sweat and milk of practically every menstruating woman. With their seedling method it was possible to differentiate between the saliva of menstruating and not menstruating women. The hypothesis of a menotoxin (also toxic to small mammals) was later supported by several investigators^{1568 1569} but the exact chemical nature of the menotoxin or the menotoxins is not known.

As far back as 1923 Patzschke and Sieburg^{1570 1571} had found that the choline content of the sweat of menstruating women was eighty to one hundred times higher than normal while at the same time in the blood the choline content increased only eight to nine times. These findings substantially confirmed by Klaus¹⁵⁷² suggest an elective accumulation and excretion of the metabolic toxin in the sweat glands¹⁵⁷³ or its production in the skin. The high choline concentration in the sweat or in the skin may well be one of the causes of menstrual exanthemas^{1574 1575}. Macht in more recent studies¹⁵⁷⁶ suggests that the phenanthrene derivatives cholesterol and oxysterol might be menotoxins. The substances are related to the steroid sex hormones. One also has to consider certain highly toxic substances in the menstrual discharge. Such toxins are formed in the endometrium¹⁵⁷⁷. The histamine content of the menstrual blood is much higher (125 to 2000 times) than that of the circulating blood¹⁵⁷⁸. Increased activity of the apocrine sweat glands during menstruation is likely. The gonadal relationship of these glands is known. (See Puberty Menopause)

The hirsutism claim that permanent waves are not successfully given during the menses but this has not been proved.

- ¹⁵⁶⁵Gröer v. H. Gilt es ein Menstruallongift? Zbl f Gynäk 43 819 1911
¹⁵⁶⁶Saenger H. J. and Lubin E. A. Phytopharmacological study of Menstrual Toxin J Pharm & Therap 22 413-466 1934
¹⁵⁶⁷Macht M. and Lubin E. A. Menstrual toxin. Mostrach f. J. d. rh. 81 394 1932
¹⁵⁶⁸Mommsen H. Menstrual toxin. Münchener med. Wochenschr 81 1459 1934
¹⁵⁶⁹Smith O. W. and Smith O. V. Studies on Menstrual Discharge. Proc Soc Exper Biol & Med 33 45-7 1934
¹⁵⁷⁰Macht M. D. I. Studies on Menstrual Toxin. Am J Med Sc 206 31-305 1913
¹⁵⁷¹Colombari L. A. Flamingo gynecological studies on menotoxin. Med. ins. Española 11 307-31 1944
¹⁵⁷²Patzschke W. and Sieburg F. Zu A. tiologi der Menstrual a. th. me. Arch f. Dermat u. Syph 146 5-62 1933
¹⁵⁷³Sieburg F. and Patzschke W. Menstruation und Cholin. Ztschr f. exper. Med. 36 324 1933
¹⁵⁷⁴Klaus K. Zu Frage des Menotoxins. Biochem. Ztschr 263 41 1935
¹⁵⁷⁵Rothman S. and Haaf F. Cholin d. Haut. Ha. d. H. u. Ch. 1 2 161-3 1939
¹⁵⁷⁶Ottensmeyer F. and Böhm A. Acetylcholin und histaminartige Stoffe im Hautdialysat. Klin. Wochenschr 14 775-776 1935
¹⁵⁷⁷Gilberti I. H. and H. and H. J. Menstrual Blood Contains Histamine in Notable Quantities. Bull Soc Ital biol per 27 234 1941

day of menstruation the next strongest in the midperiod and the lowest on the premenstrual day. Thus the greatest reactivity of the skin would coincide with the period of estrogenic deprivation. The sensitivity to tuberculin has been found greatly reduced during menstruation.¹⁵⁶³

There seems to be little or no influence of menstruation on the results of serologic tests for syphilis.¹⁵⁶⁴

Menotoxin—Popular belief has always held that a menstruating woman exerts a poisonous influence on her environment. Dough kneaded by a menstruating woman would fail to rise and fruit canned in this condition would not keep. In 1878 the British Medical Journal discussed the question whether the

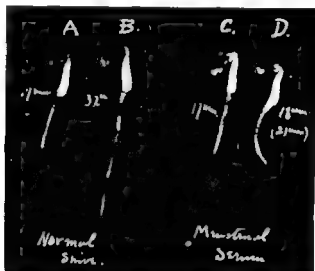


Fig. 201.—Toxic influence of menstrual serum on the growth of seedlings of *lupinus albus*. *A* and *C* length of roots at the start. *B* root after 21 hours in Rive's solution. *D* after 21 hours in 1 per cent menstrual serum in Rive's solution. The root has increased only 4 mm. instead of 15 mm. No marked inhibition of growth at *C* but much less. (From Macht, D. J. J. Pharmacol. & Exp. Therap.)

general belief was true that if a woman cured hams while menstruating the hams would spoil. Similar beliefs are found in almost all countries.¹⁵⁷⁸ The question whether cut flowers wither quicker if handled by a menstruating woman was first studied seriously by Schick,¹⁵⁴⁵ who from his experiments believed that the blood and sweat of menstruating women exert a poisonous influence on cut flowers and yeast. He found a marked difference in the life time of cut flowers held over varying periods of time in the bare hands of menstruating women compared with that of flowers handled by the same person wearing rubber gloves or in the intermenstrual period. Dough kneaded by a menstruating person rose to only half the volume of the control.

¹⁵⁶³ Petersen, W. P. and Miles, C. Relation of Menstruation to the Permeability of the Skin Capillaries to the Autonomic Tonus of the Skin Vessels. *Arch. Int. Med.* 38: 730-735, 1926.

¹⁵⁶⁴ Ingraham, N. R. and Mayer, V. R. Menstrual Cycle and the Blood Serologic Test for Syphilis. *Am. J. Syph. Con. & Ven. Dis.* 24: 23-24, 1910.

¹⁵⁷⁸ Schick, H. Das Menstruationsgift. *Wien. klin. Wochenschr.* 22: 395, 1910.

the menstrual cycle. Successful endocrine therapy is an important argument for the hormonal origin of menstrual dermatoses. The increased knowledge of allergy has done much to explain the menstrual repetitions of some skin lesions. As early as 1907 Wolff Eisner¹⁵⁰ suggested the allergic nature of *menstrual urticaria*. The regularly repeated fluctuations of a great number of substances which may have allergenic qualities and the increased reactivity provide an excellent set up for allergic phenomena. It is to the merit of Geber¹⁵¹ to have been the first to demonstrate the allergic character of some menstrual dermatoses. In a case of menstrual urticaria he took serum during the time of menstruation and injected it intravenously into the patient during the intermenstruum. This injection was followed by an outbreak of urticaria while it was not possible to elicit such a reaction with serum taken during the intermenstruum. Menstrual serum from another woman did not work in the patient and the menstrual serum of the patient did not work in another woman. The passive transfer with the method of Prausnitz and Kuestner was accomplished and desensitization by means of systematic injections of the autogenous menstrual allergen during the intermenstruum was found to be effective in a considerable number of cases.

Waldbott saw premenstrual urticaria, asthma and sneezing after a severe allergic shock caused by an injection of theelin. This observation is of great theoretical interest but so far the evidence is scant.¹⁵² Successful desensitization with ultrafiltrate of menstrual blood has also been reported. Menstrual angioneurotic edema is not rare.

The menstrual dermatoses have a definite tendency to recur in the same place as a fixed eruption. This suggests that unknown factors of the terrain play a part in the pathogenesis. It is sometimes possible to change by local X-ray treatment the reaction of such an area and to prevent the recurrence. Since many women take antipyrine for the relief of menstrual symptoms and since antipyrine is known to cause fixed drug eruptions, this possibility has to be considered. It sometimes needs the increased sensitivity of the premenstrual period to produce an antipyrine eruption.¹⁵³ It is of historical interest that the first fixed antipyrine eruption which was described by Brocq in 1904 occurred in a patient who took antipyrine for painful menstruation. The eruption was at first ascribed to her periods (Abramowitz in discussion to Throne¹⁵⁴).

In *menstrual urticaria* the eruptions are sometimes confined to the vulva and the surrounding areas. In the typical cases the picture is the same as in nonmenstrual cases of hives.

Angioneurotic edema mostly of the lips or eyelids also occurs in connection with menstruation. In one of the author's cases the first attack occurred after

¹⁵⁰ Wolff Eisner: Ueber die Urticaria vom Standpunkt der neuen Erfahrung. Über Empfindlichkeit gegen nützliche fremde Stoffe. Dtsch. med. Wch. 10: 164 17^o 1907.

¹⁵¹ Geber: II. Flück. Das neue pathologische Urticaria menstruationali. Dtsch. med. Wch. 14: 150 1921.

¹⁵² Waldbott: C. L. in Disc. to C. P. II. Allergy to Embryonal Tissue. F. tract. J. Allergy 12: 1 1941.

¹⁵³ Zary: A. Bureau: Y. and Horowitz: A. D. Dermatoses catamenses medicamentosae. Bull. Soc. fran. derm. t. syph. 44: 805 909 1937.

¹⁵⁴ Throne: II. Erythema menstruale angioneuroticum. Arch. Dtsch. med. & Syph. 21: 10 9 1930.

a childbirth and recurred menstrually for twelve years. This type of onset after pregnancy has also been observed in other cases.¹⁵³⁸

Menstrual dermatographism is known.

Pruritus vulvae menstrualis is not very rare. It is usually taken as a part of the natural congestion of the vulva during the menses and treatment is seldom requested.

Infections

The menstrual period is accompanied by a lowered resistance to many infections.^{1544 1557 1558} Many surgeons void operations during menstruation because of the increased tendency to inflammatory complications. The self-disinfecting power of the skin surface is reduced as shown by Fisher¹⁵⁵⁹ in systematic investigations with *Bacillus prodigiosus*. The serum of menstruating women shows little or no disinfecting power during the first ten premenstrual days in vitro tests with anthrax bacilli (Drexel and Keller quoted by Geller¹⁵⁶⁰). Scarlet fever, diphtheria, tonsillitis and furuncles often start during menstruation. It is known in hospitals that girls admitted because of scarlet fever and diphtheria are usually menstruating.¹⁵⁶¹ This general experience was confirmed by a study of hospital nurses. They too were often menstruating when they came down with scarlet fever.¹⁵⁶² Of 119 women in the menarche almost 50 per cent were menstruating when they entered the hospital having erysipelas. The menstrual character of the infection is more obvious if the outbreak coincides with menstruation more than once. Menstrually recurrent erysipelas is often dealt with in the older literature.¹⁶³ Cases with 50 recurrences of erysipelas have become known. Erysipelas at the time of the expected but absent menses in one case eight times in succession has been recorded. Jerusalem's¹⁵⁶³ observation of eight cases of monthly recurrent erysipelas in males has not been repeated. The whole matter of menstrual erysipelas has during the last twenty-five years¹⁵⁶⁴ found little interest. Premenstrually recurring paronychia has lately been described.¹⁵ The author saw a case of hidradenitis axillaris which over years recurred quite regularly with the menstruation. In another case a furuncle-like deep ulceration of the perineum which took two weeks to heal accompanied many periods.

¹⁵⁴⁴Hallerstein, Quincke's *Diagnos and Therapie* 9, 5. Emilina e Marchigiana di 1. gin 26 1 1913. Atte il mat W. hnschr 11 1218 1912.

¹⁵⁵⁷Spurr, D. H. The Part Played by Age and the Female Sex Hormones in the Relation to Infectious Pathology 25 6 625 1933.

¹⁵⁵⁸Spurr, D. H. McDearman, S. and Raper, J. Sex Hormones and Infection 4. Exper Med 87 1 9 1935.

¹⁵⁵⁹Fisher, S. Variations in the Disinfecting Power of the Skin During the Menstrual Cycle. Proc Soc Exper Biol & Med 28 11 333 1932.

¹⁵⁶⁰Geller, F. Infektion und menstruelle Zyklus. Münch med Wchnsch 87 1110 1910.
¹⁵⁶¹W. S. e. C. Empfindlichkeit für Infektion krankheiten und Menstruation. Zykla. Münch med Wchnsch 87 91 1910.

¹⁵⁶²Horsfall, J. e. Thard, I. and Norbmann, W. Empfindlichkeit gegen Scharlachinfektion und Menstruation. Zykla. München med Wchnsch 87 40-405 1910.

¹⁵⁶³Jerusalem, H. Beitrag zur Infektionstratologie. Erysipelas. Hft. Hft. Jahrb 190.

¹⁵⁶⁴Bullough, N. O. natl. Erysipeloiden. Menstruelle Infektion. J. J. mat 8 47 10 1930 711.

31 74.
¹⁵⁶⁵R. H. 11 1. Paronychie. Hft. Hft. vor 1. e. Menstruation. Hft. Hft. mat Wchnsch 85 286 1911.

Menstrual herpes the infectious nature of which has been established¹⁵⁹⁶ is the most common menstrual dermatosis. About three out of four cases of genital herpes in the female are due to menstruation (Bergh after Steuer¹⁴⁵³). In its appearance menstrual herpes is no different from herpes simplex. After a premonitory burning sensation of a few hours red spots appear which quickly develop into crystalline vesicles. These blisters form one or several small groups. They become pustular after one or two days then they dry up and heal without scars in about one week. The primary blister is quickly destroyed on mucosal surfaces. Here the typical appearance is a whitish or red spot with floating remnants of the blister at the edge. On the skin as well as on the mucosa the blisters may merge to form plaques. The local lymphatic nodes are often tender and slightly enlarged. Next to the genitals the lips and the chin seem to be the most common sites of the eruption. Just as the menstrual acne the menstrual herpes is often seen on the chin. Fournier¹⁵ aptly called this herpes indiscret. Eruptions on the hands on the thighs or elsewhere are much rarer. Unusual and more serious events are menstrual herpes eruptions of the cornea¹⁵⁹⁷ and of the oral and pharyngeal mucosae. The latter sometimes known as herpetic angina can be accompanied by rather severe constitutional reactions¹⁵⁹⁸. The experimental transmission of menstrual herpes into the rabbit cornea has not only been successfully performed¹⁵⁹⁹ but contact infections in man are known¹⁶⁰⁰. Menstrual herpes appears most often immediately before menstruation but in some instances during or after menstruation. The first attacks have been seen to precede the menarche several times in monthly intervals¹⁶⁰¹. It may occur at characteristic intervals in pregnancy¹⁶⁰ or if actual menstruation is disturbed by disease malformation or aplasia of the internal genitals¹⁶⁰². It may also continue to appear for a short while in the early menopause.

Menstrual acne is usually a menstrual flare up of chronic acne lesions. Possibly in connection with an increased premenstrual activity of the sebaceous glands. After the crumens the acne lesions become dormant again. Micht¹⁶⁷¹ found the menstrual series of women suffering from acne generally more toxic to seedlings than such series from women who did not have acne. The blood of young men with acne rarely exerted a phytotoxic reaction. The exacerbation of acne appears in some patients before in others during or after the menstruation often keeping this time relationship remarkably constant¹⁵⁹⁸. Some authors claim that the chin is frequently affected by menstrual acne.

¹⁵⁹⁶Lipschütz B. W. It raंतरसु हास नुबर दि Aetiologie des Zoster. II. Ueber die Mikroskopi des Impfstoffes und des genitalen Herpes exanthem nach Impfung mit Zoster A. H. f. Derm. t. u. Syph. 189 196-06 19 5

¹⁵⁹⁷And n y s A. Menstruelle Herpeside. Zbl. f. Gynäk. 49 1901 1905 19 5

¹⁵⁹⁸Lava b. Recurri g Herpetice Angina Oto-rhino-laryng. int. anat. 22 2 3 1910

¹⁵⁹⁹Kleinig H. Zbl. f. nat. Herpes (impl. x. m. menstrual) am 3 u. d. 4. Fing. r. d. r. link. n. Hand mit ex. impetiger Anstich. Blut des Handes k. n. und d. Anwesenheit des Entz. m. Zbl. 43 4

¹⁶⁰⁰Tou l. A. R. oult. I. and oult. Herpes rec. vivant trans. par un port. ur. al. de viru. Bull. Soc. Fra. c. d. d. anat. t. yph. 44 615 1903

¹⁶⁰¹W. H. Mann. 9. Herpes usual. D. utsche Arch. f. klin. Med. 88 133 1907

¹⁶⁰²Pf.emann. Menstruelle n. h. p. A. ta. d. m. t. vene. col. 1900 al. tr. D. rm. t. Wechnsch. 71 6 7 1900

¹⁶⁰³Col. mo. f. B. H. p. as a Type of Vicious Menstrual. Dublin J. M. H. 4 217 18 19 1

Hemorrhagic Dermadromes—The hemorrhagic tendency is increased during menstruation and the platelet count is lowered. Menstrual *purpura* of all degrees of severity has been known for a long time. The purpuric lesions may be petechiae or larger hemorrhagic spots. They may be universal or restricted to certain areas e.g. the lower half of the body¹⁶⁰⁴. In *purpura* as in other menstrual rashes there exists a tendency to fixed recurrence. Such fixed purpuric lesions have been seen to recur regularly e.g. around the eyes¹⁶⁰⁵ or on the thighs^{1606 1607}. Menstrual purpuric exacerbation is sometimes observed in conditions which themselves have a hemorrhagic tendency. Menstruation then provides an additional hemorrhagic factor. Cases which allow such an interpretation include one of menstrual *purpura* in a girl with mitral stenosis¹⁴⁵⁵ and cases of rheumatic fever¹⁴⁵⁸. Here also belongs the case of a petechial menstrual crop on the lower legs which appeared only while a tapeworm was present in the bowel. After removal of the tapeworm the rash failed to appear but recurred menstrually after the recurrence of the taenia. This happened four times¹⁶⁰⁸. The bleeding may occur in any open lesion.

Varicose luetic or other ulcers have often been observed to bleed during menstruation. This phenomenon about which much has been written in the last century has hardly found attention within the last generation. Another type of *menstrual ulcer* improves or heals during the intermenstruum and recurs during menstruation. More often than the menstrual ulcer has the related *vicarious or ectopic menstruation* been studied. In most of the instances the term was used incorrectly since vicarious menstruation should be called only a discharge of blood from some organ other than the uterus with suppression of the menses (Webster). This type has been called substitutional menstrual hemorrhage while for extragenital bleeding of any form occurring together with the bleeding from the uterus the term additional or complementary menstruation should be applied¹⁴⁷⁸. This mysterious phenomenon has a history in which early overestimation was followed by complete denial of its existence during the late nineteenth century. But since then so many observations have been recorded that a reserved but positive attitude has become general. It is well illustrated by a statement credited to Lawson Tait who said that he does not deny that there is such a thing as vicarious menstruation but he does deny the propriety of examiners asking the commonest cause of epistaxis and receiving the answer of vicarious menstruation with approval¹⁶⁰⁹.

The nasal mucosa is the most frequent source of vicarious bleeding. This is not surprising since menstrual swelling of certain areas of the mucosa covering

¹⁶⁰⁴John. *Purpura dysmenorrhoea* a Zbl 45 791 1913

¹⁶⁰⁵Beerman H. A Case for Diagnosis. (Cutaneous Vicarious Menstruation? Hyst. rla.) Arch. Dermat. & Syph. 33 759-760 1916

¹⁶⁰⁶Hirschberg A. Ueber die Beziehung n der Menstruation zur Haut 711 f. Gynäk. 48 1906-1907 10 4

¹⁶⁰⁷Halter. Prämenstruell rezidivieren les über Fkz m nach Balsar an i rmat tl. Zbl 48 413 1914

¹⁶⁰⁸Winkler F. Menstruell Ekchymosen durch Darmparasiten hervorgerufen. D. rmat. Wchnschr. 41 469 1917

¹⁶⁰⁹Condit W H. Compensatory (Vicarious Ectopic) Menstruation. Exnom. la Memm. a D. O. Am. J. Obst. 72 238 251 1916

the lower turbinates and the tuberculum was long ago observed by Fliess¹⁶¹⁰ who found these areas during menstruation invariably swollen hypersensitive and apt to bleed on the slightest touch

While ectopic menstrual bleeding from the gastrointestinal canal the lungs and the mammary glands have been observed relatively often sometimes under alarming circumstances the skin seems to be a rare source Condit¹⁶⁰⁹ saw a hematoma of hen's egg size develop from a small nevus on the chest in menstrual intervals after the uterus and the adnexa had been removed After excision of the nevus hemorrhage in the breast occurred Other reported sources of vicarious menstruation include old scars endometriomyoma of the umbilicus¹⁶¹¹ the nailbeds the lips and gums Bleeding from fistulae cancerous lesions and hemorrhoids must be interpreted in the same way as the menstrual ulcer^{14 14 8}

The menstrual history of these cases often reveals irregularities Puberty and still more the approaching or beginning menopause seem to predispose Several cases have been observed after hysterectomy^{14 8} Since extravasations are among the manifestations of hysteria it is not surprising that psychopathic individuals are often found among the afflicted For the sake of curiosity a twenty four year old male sexual psychopath with unusual psychic attachment to his mother may be mentioned¹⁶¹² He developed monthly cutaneous extravasations in his right arm pit

Erythemas

Besides such clinically well characterized menstrual dermatoses as herpes urticaria and purpura a great variety of transitory menstrual erythemas have been observed The simplest form is the noninflammatory erythema of the face which sometimes marks approaching menstruation It seems to be a first step towards rosacea which has a marked gonadal relationship (see Rosacea) Occasionally the congestion may involve the conjunctiva^{14 14} In some cases rosacea starts as a menstrual erythema in the blush area and becomes a stable erythema during the menopause Some menstrual erythemas have the characteristics of erythema exudativum multiforme with nummular papulo-erythematous lesions on the face neck forearms and lower legs Some are more vesicular and some show a small vesicle in the center of the red lesion Typical are the herpes iris forms while gyrate or erythema nodosum like lesions are not extremely rare^{14 11}

There is a tendency to fixed eruption More rarely the appearance is vicarious appearing only at the time of the missed menstruation Some of the cases which have been described as menstrual erysipelas probably belong to the erythemas In some cases tonsillectomy¹⁶¹³ or staphylococcic vaccine cured menstrual crops of erysipelas resembling erythemas

¹⁶¹⁰ Fliess. Beziehungen zwischen Nase und weiblich. Geschlechtsorganen. Leipzig 1907

¹⁶¹¹ F. r. N. Endometriomyoma of the Umbilicus. Arch. Path. 10: 879-880 1930

¹⁶¹² Bradley E. L. Axill. r. Menstruation in a Male. Am. J. Psy. 6: 1101-1111 1930 Zbl. 34 II 1931

¹⁶¹³ J. m. r. D. Fälle von Toxicoderma menstruale mit erysipeloidartigen Erscheinungen. Magyar Orv. 5: 199-201 1936 Zbl. 66 614



Fig 20 — Menstrual eruption resembling erythema multiforme



Fig 200. Fixed menstrual eruption of eczematous character receding almost entirely during the first menstruum

Miscellaneous—Menstrual *chromidrosis* of which substantiated reports can be found in the older literature¹⁴⁵³ has not been heard of during the last fifty years. It seems that the discolorations of the sweat either were feigned or caused by staining substances from without and not by excreted indigo as had been suggested. *Bloody sweat* has several times been seen in menstrual attacks. It is a hemorrhagic phenomenon of the same significance as other purpuric symptoms.

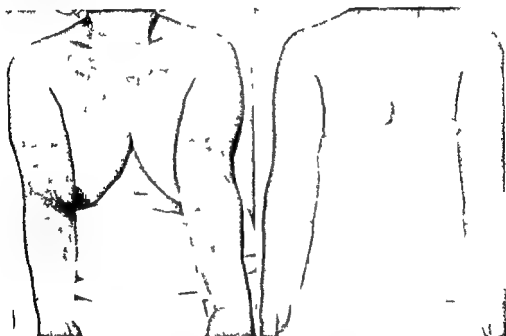


Fig. 97

Fig. 98

Fig. 97—Menstrual discoloration. (From Urbach E. Allergy Grune & Stratton Inc.)

Fig. 98—Same patient in intermenstruum. (From Urbach E. Allergy Grune & Stratton Inc.)

The menstrual darkening of freckles of the *linea alba* or of other *pigmentations* is occasionally quite marked. The greater pallor of some menstruating women or a rudimentary *chromatophoric function of the anterior pituitary* may be suggested as an explanation. No recent investigations have been published. Ruhl's¹⁴⁵⁴ observation of menstrual discoloration from gold jewelry has not found much confirmation. Naturally, one has to think of silver sulfides developed in more visible amounts by increased menstrual sebaceous secretion. Menstrual soreness of the mouth and aphthous ulcerations may become quite troublesome. In some cases these eruptions can be prevented by theelin.¹⁴⁵⁴

¹⁴⁵³Heideemann M. and Andersen H. G. Oral Manifestations of Certain Systemic Disorders. *Nat. J. Biol. & Med.* 27: 583-594, 1945.

Treatment—In all menstrual eruptions correction of any hormonal disorder should be tried. Sometimes the eruption fails to recur if normal menstruation can be restored. But this is not always true. In some cases menstruation is normal except for the rash, but the rash may yet be cured by theelin¹⁶¹⁴. Not only theelin but theelin in the first half of the intermenstruum and progesterone in the second half has been given successfully (Urbach¹⁷⁶). Other hormones or combinations of hormones such as a placenta preparation and dried adrenal glands¹⁶¹⁵ have occasionally helped.

A method of treatment which should be tried in all refractory menstrual eruptions is Geber's desensitization to premenstrual blood¹⁶¹⁶ which has been successful in a considerable number of cases. Urbach¹⁷⁶ describes the technique as follows. About 20 c.c. of blood is taken at the acme of the premenstrual exacerbation. There is some difficulty in determining the right time since much seems to depend on getting the most potent allergen. The blood is centrifuged and the serum poured into a rubber capped bottle. After 1:10,000 of merthiolate has been added the serum is stored under refrigeration. Then 0.2 c.c. of serum is injected intracutaneously every second day. The injections are given four successive times into the same site. The site of injection is changed after eight to ten days. Lehner and Rajka (after Urbach¹⁷⁶) inject 0.4 c.c. daily into two areas in corresponding symmetrical sites. While this method was originally used in menstrual urticaria it later proved to be effective in other menstrual dermatoses and complications also e.g. in menstrual trigeminal neuralgia¹⁶¹⁷.

¹⁶¹⁵Adrenal Substance in Dermatoses Which May Have a Menstrual Factor Arch. Dermat. & Syph. 31: 865, 1935.

¹⁶¹⁶Geber H. Desensibilisationsversuche bei Menstruationsintoxikationen. Med. Klin. 31: 103, 1904, 1935.

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CHAPTER XXIII

PREGNANCY

The fertilized ovum after its implantation into the uterine mucosa causes profound changes in the hormonal balance. Within a few days after the first missed period the anterior pituitary like hormone (chorionic gonadotropin) from the placenta increases in the blood as well as in the urine and reaches a level many times higher than normal after about sixty to ninety days. This peak subsides and remains at a lower but still elevated level until delivery. The estrogen content of the blood and urine increases progressively from the second month until near term. The progesterone level rises until after the fifth month when the corpus luteum undergoes involution. The ratio of the estrogens changes and may assume an abnormal pattern in pre eclampsia.^{151b} With the expulsion of the fetus and placenta a rapid return to the pregravid state ensues with a slump in the normal production of hormones.^{151 1617}

It is natural that the hormonal upheaval of pregnancy is associated with profound changes in the entire endocrine system.

The anterior lobe of the *pituitary* increases to two and one half times its usual weight and there are characteristic microscopic changes. The large amount of pituitary gonadotropic hormone in the blood and urine is well explained by this hypertrophy. This may account for various stimulations of growth of the skin and its appendages.

After the third month the *thyroid* gland increases in size in almost all cases and its activity is stepped up. Iodine moves from the thyroid into the blood reducing the glandular iodine level about one half. The basal metabolic rate is often raised. If the thyroid is unable to meet the increased demand for thyroxin hypothyroidism may develop. The hyperthyroidism of pregnancy may explain certain sensations of heat, hyperhidrosis and erythema.

The *parathyroid* glands too are stimulated probably due to the high demand for calcium for the child's skeleton. The calcium deposits in the mother are drained. The blood calcium level is lowered. Inability to meet the increased requirement may cause a state of hypoparathyroidism with tetany. The ovaries swell and the follicles continue to develop but fail to ripen. The *corpus luteum* provides an uninterrupted supply of progesterone needed for implantation, the prevention of uterine contraction and the formation of the decidua. After the first half of the pregnancy the corpus luteum undergoes involution to prepare for the termination of pregnancy. Some of its functions are taken over by the pituitary and the placenta. The increased secretion of estrin changes the microscopic picture of the vaginal smears. The epithelial cells increase in size during the first months. Later they become smaller again, so called oyster shaped cells appear and leukocytes abound. Just before labor the desquamation of the

¹¹ Freed S C. *Glandular Physiology and Therapy*. Chicago 1941 American Medical Association

vaginal mucosa almost reaches denudation. The adrenal cortex hypertrophies during pregnancy to meet the greater demand. That the demand is greater has been shown by the fact that adrenalectomized cats need more cortical extract for survival during pregnancy than when nonpregnant. The lowered glucose tolerance of pregnancy is perhaps caused by a hyperactivity of the adrenal medulla though it has been ascribed to pituitary, pancreatic liver and renal factors. In the liver glycogen disappears from the central portion of the lobules and bile stagnates in the biliary channels.

During the latter part of pregnancy a great amount of nitrogen is stored in the maternal system beyond the need of the fetus. The blood NPN falls. Albuminuria is common.

The fat content of the blood increases after the third month giving the blood serum a cloudy appearance. The alkalinity of the blood is increased. Cholesterol is increased in the blood and in the adrenal glands. The blood cholesterol (not the cholesterol esters) increases about 100 per cent.¹¹³ There is a retention of sodium potassium magnesium and sulfur and the excretion of iron and phosphorus is decreased. The retention of most of the minerals exceeds the needs of the growing fetus.

Normal Skin Changes.—The skin responds to pregnancy in many ways. According to the majority of the observers the perspiration is increased especially towards the end of the pregnancy. Extreme degrees of hyperhidrosis have been seen¹¹⁴ in this period. The increase of sweat secretion may take some strain off the kidneys. The urea may rise in the sweat with increasing renal insufficiency. Chlorine increases in the sweat during the first half of the gestation but decreases later. In toxemia it is greatly reduced.¹¹⁵ Protein appears in the sweat of the pregnant women.¹¹⁶

An actual hypertrophy of the sweat glands which had been claimed earlier¹¹⁷ does not seem to have been confirmed in more recent investigations. It has been suggested that the growth of the sweat glands in pregnancy is part of the trophic tendencies caused by the pituitary changes.¹¹⁸ The perspiration insensibility decreases with the progress of the gestation but increases during the puerperium. The loss of water through the skin is particularly low in toxemia.¹¹⁹

The apocrine glands the gonadal relationship of which has been mentioned in the chapter on Puberty probably cease to secrete during pregnancy.¹²⁰ The secretion of the sebaceous glands increases during the latter half of gestation.

Schaaf V. Der Lipidstoffwechsel. Zbl. 23. 1-32. 193. 213. 1970.

¹¹³ J. O. B. Hyperidrosis gravidarum. Zbl. f. Gynäk. 59. 2787-7769. 1914.

¹¹⁴ G. A. L. The skin changes in the toxemia of pregnancy. J. Obst. Gynaec. 27. 374-380. 1931.

¹¹⁵ Connell V. Le prolane sal. J. Obst. Gynaec. 28. 49-57. 1931.

¹¹⁶ R. F. A. The sweat apparatus in the human body. J. Obst. Gynaec. 1931.

¹¹⁷ G. A. L. The skin changes in the toxemia of pregnancy. J. Obst. Gynaec. 27. 374-380. 1931.

¹¹⁸ P. F. A. The sweat apparatus in the human body. J. Obst. Gynaec. 1931.

¹¹⁹ G. A. L. The skin changes in the toxemia of pregnancy. J. Obst. Gynaec. 27. 374-380. 1931.

¹²⁰ G. A. L. The skin changes in the toxemia of pregnancy. J. Obst. Gynaec. 27. 374-380. 1931.

This seborrhea is especially marked during the last five days¹⁸⁶ and during labor. Soon after delivery both hyperhidrosis and seborrhea return to normal. It is interesting that the seborrhea of pregnancy is only rarely accompanied by acne.¹⁸⁷ Usually, existing acne is improved. This suggests that not seborrhea but other factors (comedones) are the cause of juvenile acne.

Implantation of particles of normal skin of pregnant women into rats and infantile mice produces the same changes as the pregnant woman's urine. It does not elicit the Allan Doisy reaction. This proves that prolactin and not estrogen is the active principle. The prolactin is apparently stored in the skin. Skin which has been rendered anemic is not less and skin with the pigmentation of pregnancy is not more effective than normal skin.¹⁸⁸

The epidermal mitoses are more numerous in pregnancy at least in the guinea pig.¹⁸⁹ This indicates a stimulated growth which manifests itself in an occasional thickening of the skin in hypertrichosis and in the development of small neoplasms. The lips may appear thicker, the features coarser and the facial expression may well resemble an early stage of acromegaly.

Pigmentation—During pregnancy certain areas of the skin which already have a tendency to increased pigmentation receive a stimulus to produce more pigment than in the nonpregnant state. Scars, particularly those from abdominal operation, often take part in the pigmentation. Brunettes become much more heavily pigmented than blondes. Generalized melanosis and darkening of larger but circumscribed areas adjoining the well known physiological sites of pigmentation, although a little more common in pregnant hyperthyroid women,¹⁹⁰ is extremely rare. The linea alba, or more correctly the midline of the abdominal skin, usually becomes pigmented in the third month of pregnancy but sometimes much later, especially in blondes and multiparae.¹⁹¹ This linea fusca or *linea nigra* as it is often called, extends from the mons veneris to the navel and, though less often and less pronounced, into the epigastric region. The line is about one third of an inch wide and varies in color from light greyish brown to deep brown or black. If it extends to the epigastric area it often forms a one half to one inch wide brown ring around the navel which is called the umbilical areola of Montgomery. The black line is present in 94 per cent of pregnant women. It is occasionally missed in obese women and in very light individuals rarely in the darker pigmented women. The pull of the ligamentum teres of the liver sometimes causes a deviation to the right of the supraumbilical part, thus producing a bayonet shaped line.

The areolae of the mamillae darken more intensely than the linea nigra, the degree varying again with the color of the hair. There is a certain amount of darkening around the areola proper. This secondary areola consists of a network of brownish lines surrounding the lighter follicles. The secondary areola

¹⁸⁶Flores M. La seborrea en la embarazada. Arch. de Soc. Biol. 27: 71-86, 193.

¹⁸⁷Stitz L. Schwank schwacht to Kos n und Ha t. Zbl. 27: 3, 19.

¹⁸⁸Looser A. Die Haut als H rmo tr g r ind r s hwang schwacht. Zbl. f. Gyn k. 86: 115-193.

¹⁸⁹Loeb L. and Haven F. L. The Relation Between States of the Sex Organs in the Female.

Gyn. a-pig. a d th C h I proliferation i the Epidermis. Anat. Rec. 43: 1-6, 190.

¹⁹⁰Fleisch G. La pigmentation k type addisonn dans la maladie de Basedow. Rev. f. anc. d'endocrinol. 6: 193-208, 19.

though being a sure symptom of pregnancy does not appear before the fifth month¹⁸³¹

The hyperpigmentation of the vulva can reach extreme degrees. The edges of the labia minora are intensely pigmented. The discoloration may



Fig 709 Melanosis of pregnancy. Note deviation of pigment d line alia to the right caused by pull of ligamentum transversale. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

extend beyond the vulva to the perineum, to the inner aspects of the thighs and around the anus. Rarely old scars and striae become pigmented. The sensitivity to light increases in pregnancy, which causes more ready tanning.¹⁸³⁷

The number of noticeable pigmented spots increases in about 25 per cent of the pregnant women. Freckles or lentigo-like spots appear or become more pronounced.^{1832, 1833} An unpigmented mole may become pigmented.

¹⁸³¹ K. Brer. In Haffan J. and Pettit E. *Biological and Pathological Changes in Women* vol. 6. D. Appleton, 1936. Urban & Schwarzenberg, pp. 704-709.

¹⁸³² Jordan A. *Chlamydia facialis bei jungen Mädchen in Schwangerschaft und Frauen und Mädchen*. Dermat. Wechnsch. 98: 336-340, 1933.

¹⁸³³ Goldsmith W. N. *Pigmentation*. Brit. J. Phys. Med. 21: 43-46, 1936.

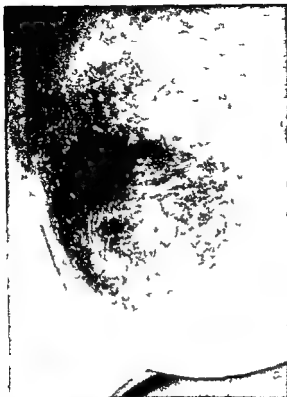


Fig 210 —Pigmentation of breast in pregnancy



Fig 211 —Chloasma persisting after pregnancy —Irregular menstruation

'Quæ utero gerunt in facie maculam habent' Those who are pregnant have spots on the face. This was known as a fact to Hippocrates but in the nineteenth century¹⁶² the connection of *chloasma* with the uterus was still the subject of much controversy. It was either claimed that it had nothing to do with the uterus or that it was identical with *tinea versicolor*. *Chloasma* is present in 74 per cent of all pregnant women in the later part of the gestation. Only one third of the cases are marked, the rest are more often pale than pronounced depending much on the color of the skin and hair. (F. A. Kehler and Karl Hoffner after E. Kehler¹⁶³) The color may be deepened by exposure to light.¹⁶⁴

The *chloasma* of pregnancy consists of sharply outlined often jagged yellow brown or grayish spots. They are symmetrical and follow certain patterns.¹⁶⁵ They either appear as scattered small spots on the cheeks and no color mask like discoloration which leaves the lids, the surroundings of the eyes, the preauricular areas, parts around the mouth, the temples and almost always a narrow strip along the frontal hairline free. In another type the temples and the zygomatic areas are dark while a trapezoid area in the center of the forehead remains light.¹⁶⁶ Transitional types between these patterns occur.

Chloasma usually disappears within a short time after delivery. The first menstruation seems to stimulate the bleaching. Not infrequently the spots fail to vanish for a long time even for many years. *Chloasma* has even been seen to persist in the menopause. (Muratori after Sézary and Duruy¹⁶⁷)

Chloasma like pigmentations are not exclusively seen in pregnancy. They have been observed in young girls, nonpregnant women and in men. *Chloasma periorale virginum* is a type of stubborn *chloasmatic* pigmentation in the lips of young girls.^{167, 168} The nonpigmented narrow strip separating the *chloasma* from the vermillion border which originally was described is characteristic in this condition can be seen in many perioral pigmentations e.g. in perioral vitiligo.

The pigment of pregnancy is melanin. As such it is iron free¹⁶⁹ and in its histological characteristics is no different from melanin deposits in other conditions.

The cause of the pigmentations of pregnancy is seen by some authors in the uterine cortex if hypertrophy.^{169, 170} There is no doubt about the existence of adrenic changes in pregnancy and about the connection of pigmentations with the adrenals but it has not been proved that just the pigmentations of pregnancy

¹⁶² 'Si iron ay' Schwangerschaft pigmentierung u. d. Chloasma. Handb. d. H. u. Gk. 2. 90. 1913.

¹⁶³ 'K. J. J.' Form u. Entstehung d. Chloasma uterinum benannt n. Hyperplasmie d. Adren. des Endo. d. Endo. Ztschr. 88. 1. 19. 1930.

¹⁶⁴ 'Zary' S. and Duruy A. Chloasma. Nouv. ell. pratiqu. dermatol. gynec. vol. 6. 1a. 1930.

¹⁶⁵ 'K. J. J.' Chloasma periorale virginum (Ebor). Zbl. Bl. 17. 19. 4.

¹⁶⁶ 'Tscham' F. Histologic u. Hist. tocht. m. d. Gynäk. d. Endo. d. Endo. Arch. f. Gynäk. 169. 3. 1910. 1930.

¹⁶⁷ 'K. J. J.' Chloasma periorale virginum (Ebor). Zbl. Bl. 17. 19. 4.

¹⁶⁸ 'K. J. J.' Les dermatoses les troubles de la grossesse. Gynec. et Obst. 21. 4. 7. 1930.

are caused by the adrenal influence. It has been shown^{14, 144, 145} that in animals as well as in man pigmentations identical to those in pregnancy can be produced by the implantation of ovaries or by the injection of large amounts of estrogen under certain conditions. In pregnancy there exists a tremendous increase of the estrogen level. The work of Bloch has so far given the best explanation for the pigmentations of pregnancy. The pregnancy of one of a pair of siamese twins provided a unique observation. The nonpregnant twin developed chloasma as well as the pregnant one. Both chloasmas were concordant. (Hübner after Meirowsky¹⁴⁴). This proves a hormonal or humoral cause of the pigmentation and at the same time the existence of certain local possibly hereditary factors necessary for pigment formation. A hereditary factor in chloasma uterinum without pregnancy is established¹⁴⁷.

It has been suggested that the vitamin C deficiency in pregnancy may have something to do with chloasma. Vitamin C is known to exert an inhibitory influence on melanin formation at least under experimental conditions (see Addison & Disea¹⁴⁸). However it has not been established that prophylactic administration of Vitamin C in pregnancy prevents or heals chloasma^{146, 147}.

Statistical and tintometric investigations in a large number of pregnant women¹⁴⁹ seem to corroborate the belief that heavy pigmentation is associated with an undisturbed pregnancy. It is statistically correlated with less vomiting, vigorous labor and less danger of atonic hemorrhage and perineal lacerations. On the other hand Grossmann and Schoneberg¹⁴⁹ based on laboratory studies deny any metabolic differences between heavily pigmented and nonpigmented pregnant women and attach no diagnostic or prognostic value to this phenomenon.

Hypertichosis—Occasionally the hair growth of the face and some other areas increases considerably during pregnancy. This was already known^{144, 149, 150} when Halban¹⁵¹ (1906) discovered that hypertichosis is a physiological phenomenon of pregnancy. It is ordinarily so slight that it passes unobserved. The light down on the face¹⁴⁶ as well as on the arms, legs and the abdomen becomes a little heavier and darker. Along the linea nigra it may or may not lead to a

¹⁴⁴ Lipschütz A. Über den Ort der Pigmentbildung. *Virchows Arch. B. Path. Anat.* 276: 678-680 1930.

¹⁴⁵ Bloch H. and Goldberg C. Die Tracht der Schwangerschaftshyperpigmentierung. *Klin. Wchnsch.* 12: 734-735 1933.

¹⁴⁶ Bloch H. Erzeugung der Schwangerschafts-Hyperpigmentierung (Chloasma Linæ albae) beim Menschen durch Injektion des Ovarialhormons (Oestroglandol). *Zbl. B.* 15: 1933.

¹⁴⁷ Bloch H. Die hormonale Beeinflussung der Pigmentbildung. *Zbl. B.* 44: 519 1933.

¹⁴⁸ Forbes Th. R. A study of the hair changes in pregnancy. *Endocrinology* 20: 465-469 1934.

¹⁴⁹ Techner E. Chloasma Gravidarum and Vitamin C. *Klin. Wchnsch.* 12: 11: 1614 1934.

¹⁵⁰ Hruszcek H. Chloasma gravidarum.—Vitamin C. *Münch. med. Wchnsch.* 84: 1336 1937.

¹⁵¹ Halban H. Studies on Skin Pigmentation During Pregnancy. *Jap. J. Obst. & Gynec.* 11: 43-44 & *Zbl. B.* 31: 67. *Jap. J. Obst. & Gynec.* 12: 365-370 19 & *Zbl. B.* 34: 793. *Jap. J. Obst. & Gynec.* 13: 374-377 377-380 1929. *Zbl. B.* 35: 7 & 8.

¹⁵² Jorjani A. Ca. of Hirsuties Gestationis. *New York M. Rec.* 1875.

¹⁵³ Hegar A. Zur Abnormen Haarigkeit bei der Geburt. *British J. Gynaec.* 4: 21 1901.

¹⁵⁴ Halban H. Über ein bishe nicht beobachtetes Schwangerschaftssymptom (Hypertichosis graviditatis). *Wien. klin. Wchnsch.* 19: 1906: 20 1907.

¹⁵⁵ Cedreux A. Hypertichosis superciliarum et in fronte in graviditate aperiens. *Acta de mat. venerol.* 20: 704 1929.



Fig. 12 —Hypertrichosis of pregnancy (From Stoddard F J Am J Obst & Gynec 1915)



Fig. 213 Same patient as shown in Fig. 212 4 months after delivery. Hypertrichosis which was so marked in pregnancy has completely disappeared. Eyebrows appear less heavy (From Stoddard F J Am J Obst & Gynec 1915)

pronounced male type of hair distribution¹⁶³ Occasionally a marked hair growth appears just in the midline quite different from the male distribution Halban¹⁶⁴ showed that two weeks after shaving the abdomen of a pregnant rabbit was covered with thick hair while hardly any growth could be noticed in the controls It took less than half the time to restore the full hair of a pregnant rabbit than was necessary in the nonpregnant Similar observations have been made in other domesticated animals However the increased growth stops before the parturition¹⁶⁴ The hypertrichosis of pregnancy usually disappears shortly after delivery and sometimes at the time of the first menstruation but it may reappear in subsequent pregnancies It is suggestive to relate the hypertrichosis of pregnancy to the hypertrophy of the adrenal cortex* Pituitary and thyroid stimulation may play a part

A pregnancy test based on the sulfur content of the hair compared with that of nonpregnant women has been described by Kossiakoff¹⁶⁵ It has not found enough confirmation

Alopecia areata has a tendency to disappear in pregnancy but may recur shortly after parturition¹⁶⁶ In some cases alopecia areata began shortly after pregnancy A seemingly paradoxical and rare phenomenon is the disappearance of hypertrichosis of the upper lip during pregnancy and its recurrence after parturition¹⁶⁶

The daily growth of the *nails* during pregnancy has been found to be increased from 0.13 to 0.16 mm¹⁶⁶⁷

Striae, Including Those Not Related to Pregnancy—Striae are stripe shaped lesions which by their form and arrangement across distended skin immediately show that mechanical tension is a factor in their pathogenesis Though by far most common in pregnancy they occur in other conditions in most of which the skin is or has been under mechanical strain caused by enlargement of the volume of tissue which it covers

Since the striae of pregnancy are the most common example of striation the whole phenomenon may be discussed in this chapter The striae of pregnancy are linear or somewhat wavy stripes of one to five inches (2.5 to 13 cm) in length and one quarter to one half of an inch (0.6 to 1.2 cm) in width Fresh striae are deep pink or purple the latter color not being due to hemorrhage as one might expect but to the transparency of the thinned skin In the early stage they look like the marks of whip lashes which in French are called *vergetures* This expression is occasionally used for striae Gradually the thin transparent skin is replaced by a denser scar like tissue of pearly white color Sometimes old striae are brown with pigment Striae never disappear completely but they may

¹⁶³Goldfarb¹⁶³ found the 17 keto steroid in the urine of his cases to be 8% to 10% mg in the twenty four hour urine compared with the normal pregnancy range of 3 to 6.5 mg

¹⁶⁴Goldfarb F J. Hypertrichosis in pregnancy. *Am J Obst & Gynec* 49: 417-422 1945

¹⁶⁵Hen I. Hypertrichosis in pregnancy. *Ztschr f d ges pr Med* 104: 182 1938

¹⁶⁶Afa awlesky I M. Le diagnostic de la grossesse au debut par la réaction chimique des cheveux. *Gynecol et Obst* hebdomadaire p 36 1934

¹⁶⁶⁷Lombolt H. Hypertrichosis an der Oberlippe und ihr Schwund während der Gravidität. *Klin Wchnschr* 12: 107-109 1934

¹⁶⁷Halban J and Spitz R M Z. Leber das gesteigerte Wachstum der Nägel in der Schwangerschaft. *Monatsschr f Geburtsh u Gynäk* 82: 5-31 1929

become quite inconspicuous. The surface of fresh striae is smoother than the normal skin, sometimes slightly wrinkled transversely or diagonally, so that diamond-shaped figures are formed.

Fig. 214

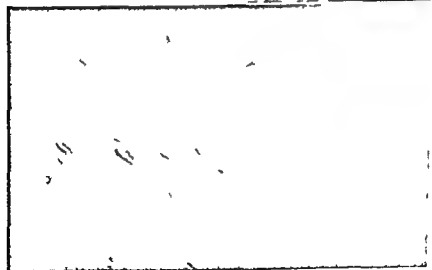


Fig. 215

Fig. 214. Striae of pregnancy.

Fig. 215. Obliterated striae of pregnancy.

The palpating finger receives the impression of emptiness and decreased resiliency. This is caused by the lack of the elastic fibers the skin skeleton. Some striae on the lower abdomen and the sides are raised and more palpable.¹⁶⁹

The striae caused by pregnancy are usually but not always symmetrical. They are arranged in several groups. One group of longitudinal striae surrounds the navel extending farther downward than upward. A second less pronounced system occupies the lower abdomen its striae often crossing those mentioned before. A third system runs longitudinally over the hips down to the thighs. A fourth large group forms concentric and approximately circular figures around the sacral area. This group may extend upward as far as the eighth dorsal vertebra. Other mostly smaller bunches may surround the popliteal and elbow areas and cover the shoulders and axillary folds. Their direction is longitudinal. Finally the breasts show striae arranged in radial fashion around the areola.¹⁷⁰

¹⁷¹ It should be kept in mind that striae are not always caused by pregnancy. This fact is occasionally of some forensic importance. Striae from obesity are mostly found in longitudinal groups on the upper arms hips and thighs. Some surround the navel. The striae produced by fast growth during adolescence run transversely. They cross the thighs and to a lesser extent the hips and the lower back. The striae following typhoid fever dysentery and other infections are most frequently found across the lower thighs just above the knees. Generally striae develop in a direction perpendicular to the maximal tension. If a limb grows longer the striae appear transversely if it increases in thickness the striae are directed longitudinally. Irregular tractions produce irregular striae e.g. those one observes occasionally on the side of the chest opposite to a pneumothorax.¹⁷²

Striae graviditatis occur in at least 90 per cent of all pregnant women though in very different degree (Credé and many other authors after E. Kehrer¹⁷³). These high figures were derived from observations on white European women. Some but not all pigmented races for instance the women of Java and the negroes of West Africa are reported to develop striae only very rarely.¹⁷⁴ This may be partly due to racial peculiarities or to the massaging of the pregnant abdomen a custom which has found its advocates in the western world.¹⁷⁵ Barfurth claimed that fifteen to thirty minutes of daily gentle kneading of the abdominal skin prevents formation of striae. This treatment is also supposed to bring about a better contraction of the abdomen after delivery. The recommendation does not seem to have been widely followed.

The histology of the striae shows that the lesion is situated in the deeper layers of the cutis. There is a marked basophilic reaction and changes in the shape and texture or complete atrophy of the elastic fibers within the striae and an increase in the pathological fibers at the border of the lesion. Here some of them look

¹⁶⁹ Fontana H. Pyrexia y Complicaciones—Atrophic Stri. Ann di ost. ginec 61: 14, 1919.

¹⁷⁰ Bönauer St H. Atrophie d. Haut. In A. Taubert's Die Haut u. i. Geschlechtskrankh. n. vol. II. Berlin 1935. Urban & Schwarzenberg pp. 718-74.

¹⁷¹ Oppenheim M. Atrophie u. Handb. d. H. u. G. 5: 500-716 1931.

¹⁷² Comby J. En as d. y. gestures thoraciques unilatérales. Bull. t. mém. Soc. méd. d. Hôp. d. Paris 42: 1005 1907.

¹⁷³ Stratz, C. H. Leber'sche Hauterkrankheiten. Zbl. f. Gynäk. 26: 431 1917.

curled as if they had given way to the tension and snapped back. Inflammation has occasionally been noticed in the early stages. Like the blood vessels they are arranged in the direction of the tension. It seems as if the tension does much harm to the elastic and only little to the collagenic fibers. The microscopic findings can be interpreted as evidence of chemical as well as mechanical damage to the elastic fibers. Lately Fontana¹⁰ has described striae with a marked inflammatory reaction and lack of distention as expressed by the normal wavy appearance of the papillae.

The microscopic evidence furnishes some support to the opinion of the majority of modern authors that the mechanical tension however necessary it may be is *not the only factor* in the pathogenesis of striae. This belief is based on a variety of observations. Some pregnant women develop striae in spite of relatively little tension others never do no matter how extended their abdomens become. Of possible significance is the case of a pregnant woman who acquired striae over the biceps muscle of one arm from carrying books while the same exertion did not cause striation when she was not pregnant.

Tension does not always lead to striae. There are many cases of enormous cysts ascites and edema with extreme stretching of the skin but without striae. While the fat boys with Frohlich's syndrome rarely show striation the obese patients with Cushing's syndrome always have them and just in this condition the striae not only are the widest ones one can observe but they are already very marked when obesity has not reached degrees which could easily explain cutaneous tears. In men striae are found in 6 per cent^{10a}. Men are probably less apt to develop striae than women if one does not consider the striae of pregnancy. The pronounced striation in the basophilic adenoma of the anterior pituitary and the pituitary changes in pregnancy suggest a pituitary hormonal factor. Pseudoxanthoma elasticum which is clearly a disease of the elastic fibers has been seen appearing in crops during two pregnancies of a patient.^{10a}

The loosening effect of pregnancy on the elastic tissue of the pelvic ligaments which is said to be of pituitary origin may be caused by the same agent which has an affinity to the elastic fibers of the skin. The kyphosis which commonly develops in Cushing's syndrome may also be due to the same elastica loosening factor as the striae. In the cases of striae caused by adolescent growth the actual tension of the skin is not great compared with other conditions of stretched skin which do not lead to striation. Adolescence is a period of increased pituitary activity. Infections too may have a damaging influence on the elastic fibers. Striae are known to occur though only in a small minority of the patients mostly adolescents after typhoid fever dysentery paratyphoid in the course of typhus rheumatic fever leprosy syphilis and other infections. Almost always the patients have been bedridden over a long period of time. In these cases the striae are found on the back and often above the patella which may have something to do with lying in bed with the knees bent. In pulmonary tuberculosis

¹⁰Glauberstein H. A. Contributor to *Biologische des menschlichen Embryos* Ann. 101 1934 1 179
 10a *Wiener Z. f. Naturforsch.* 1934 1 179

^{10b}Wien. Z. f. Naturforsch. 1934 1 179

striae have often been observed on the side of the thorax opposite to the side of the main lesion. Increased movement and coughing could explain this localization but this apparently well established fact was not confirmed in twelve cases of striae thoracicae among 5800 tubercular patients¹⁶⁶⁵. Szánto¹⁶⁶⁶ in his large series always found them on the side of the pulmonary involvement.

Transverse striae crossing the spine below the level of the shoulder blades are relatively common in spondylosis deformans but are supposed to be rare in spondylitis¹⁶⁶⁷.

Several authors have tried to correlate the color of the hair with the formation of striae. The results are contradictory which probably means that there is no relationship. The older primipara is less apt to develop striae than the younger one. The same is claimed of the more virile type¹⁶⁶⁸ and of the short asthenic megalosplanchnic women^{1669 1670}. The more striae a woman develops in pregnancy the more likely she is to suffer perineal lacerations but no relation to the labor pains has been established¹⁶⁷¹. It is possible that a hereditary factor has influence on the development of striae. Leven¹⁶⁷² saw lumbar striae in three of nine siblings and Siemens¹⁶⁷³ twice saw concordant striae in nulliparae who were identical twin sisters. In the unique case of pregnancy of one of siamese twins the nonpregnant one did not develop striae (Hubner after Siemens¹⁶⁷³). Horneck¹⁶⁶⁹ observed the appearance of striae after the injection of adrenal cortical extract.

The elasticity of the skin in normal pregnant women is about one third lower than normal. This lack of elasticity is still more marked in the presence of clinical edema and albuminuria^{16 4 16 5}. It starts in the third month and reaches its peak at the end of pregnancy. Though edema may lower the elasticity of the skin it does not increase the tendency to formation of striae.

Edema—A slight increase in the amount of fluid in the skin and in the subcutaneous tissue of the pregnant women must be considered normal. This is to a large extent due to the retaining influence which estrogens and progesterone exert on sodium and water metabolism¹⁶⁷⁶. Surgeons know that the cleavability of the tissues is increased during pregnancy. The butchers know that it is easier

¹⁶⁶⁵ Hoffman R I. Striae Distensae in the Skin of Consumptives. *Tubercle* 2: 349-352, 1911.

¹⁶⁶⁶ Szánto C. Endokrin bedingte Dermatosen bei Lungentuberkulose. *Zbl.* 40: 734.

¹⁶⁶⁷ Sathe O and Winkel W. Striae distensa cutis. *I. Wkn Arch f. d. Med.* 29: 351-384, 1903.

¹⁶⁶⁸ Yang J. Hwang schaffststreifen und Konstitution. *Zbl. f. Gynäk.* 50: 1749-1758, 1906.

¹⁶⁶⁹ Nardelli L. Il p obalito fatto e doeri o nella patol. nesl. d. llo. st. fac. cutis atrophicae. *Endoc. inol.* 1: 101-103, 1911.

¹⁶⁷⁰ Nardelli L. Le striae cutis atrophicae. *Glor. Ital. di dermat. e sif.* 78: 607-617, 1935.

¹⁶⁷¹ Rodewald M. Striae gra. Marum. *Ach. f. Frauenh.* 11: 199-206, 1913.

¹⁶⁷² Leven M. Streifung lehnung d. r. Regio sacro-lumbal. *Dermat. Wehnch.* 94: 333-336, 1931.

¹⁶⁷³ Siemens H. W. Die Vererbung in der Aetiologie d. r. Hautkrankh. in a. Handb. d. H. u. Gk. 3: 166, 1931.

¹⁶⁷⁴ Decio C. Al. uno r. erche di lastom trla cutan. a nel campo o. t. t. lco-ginecolog. o. RI. Ital. di ginec. 11: 534-546, 1930.

¹⁶⁷⁵ Ans. Im. F. L. t. das V. erhalten de. Haut lastizität währ. d. d. n. Schwang. schaft. Diss. 1930. Frankfurt a. M. *Zbl.* 11: 70.

¹⁶⁷⁶ Taylor H. C. Jr. Warr. R. H. C. a. d. Wel. h. L. A. Relati. ship of E. t. o. gens. a. i. Progesterone to Edema of Normal and To. mic Pregna. cy. *Am. J. Obst. & Gynec.* 45: 547-569, 1943.

to skin a pregnant animal than a nonpregnant one. Both observations may be explained by the serous imbibition of the tissues.

While a certain pre edematous condition is physiological in pregnancy clinically noticeable edema of the legs occurs in 28 per cent of all pregnancies (Hoffner after Scheuer¹⁸²).

McClure and Aldrich's method of testing the skin for impending or not yet palpable edema by measuring the disappearance time of a welt produced by the intracutaneous injection of 0.2 cc of 0.8 per cent NaCl solution showed that in pregnancy the disappearance time is almost always shortened.¹⁸⁷ The reduction of the disappearance time is in direct proportion to the degree of edema and can be used as a prognostic sign.^{187 187a} The disappearance time is shorter in the legs than in the arms. It is considered to be an unfavorable sign suggesting impending eclampsia if the stasis of a pregnant woman does not disappear on bed rest.^{188b}

Severe edema of the vulva is a rare complication of pregnancy being encountered three times in 12 000 pregnancies. The trouble may repeat it self in subsequent pregnancies. The swelling may reach the size of a man's head and may even necessitate cesarean section.^{189 191}

Circulation — During pregnancy the peripheral circulation is marked by *vasomotor instability*. Pallor quick changes in the facial color and sensations of heat and cold in the extremities are common particularly in the later months. Red or white dermatographia is almost always noticeable though varying in intensity.^{19 1812} This widely held opinion has lately been contested (Piccone after Vignes¹⁸⁴). Dermographia is most noticeable on the back, the sternal area and on the abdomen above the fundus uteri.^{144 185} The reaction is reported to be weaker in heavily pigmented skin.

Direct observation of the peripheral blood circulation by *capillaroscopes* has shown that the flow of blood in the capillaries of the lower legs and of the fingernails is often slowed down. Segmentation or complete stasis or even regurgitation of the blood from the venules to the arterioles has been observed more often than in controls.^{189 189a 189b} It is considered to be an unfavorable prognostic

¹⁸⁷Obstet. J. Die Quaddelreaktion als Frühdiagnostikum der Schwangerschaft. Arch. f. Gynäk. 123 163 19 4.

^{187a}Lab. & F. Intracut. small salt solution Test in Normal and Tox. mi. Pregnant. Am. J. Gynec. & Obst. 43 40-43 1920.

¹⁸⁸Hornung R. Das Verhalten d. intracutanen Normosalquaddel bei Schwangeren. Zbl. f. Gynäk. 61 30 19 7.

^{188a}Hilfmann H. Über das Ödem der Schwangerschaft. Zbl. f. Gynäk. 45 1381 1361 19 1.

^{188b}Kam. H. F. Phantasi. vulvae und Schwangerschaft. Zbl. f. Gynäk. 61 10 19 1920.

¹⁸⁹Joakim A. Vulva Ödem Macy Gynecology 6 5 1917 711 86 143 1927.

^{189a}Jordan A. Hautrötung bei Schwangerschaft. Zbl. f. Gynäk. 61 309.

^{189b}Vignes H. Pregnancy Complications. Evolution of Vaginal Lesions in Pregnancy. Arch. d. mal. du coeur 32 474-480 1921.

^{189c}Ilvén I. H. d. mögast. mo nella madre e n. l'incanto e r. l'at. coristat. n. m. o. f. tati. Attid. 4. conf. f. f. for. H. in. f. na. 2 472 391 1921.

^{189d}Hilfmann H. Capillaroscopia durante la gravidanza. Zbl. f. Gynäk. 45 10 19 1920.

^{189e}Hilfmann H. Haupt W. and f. ttekov. H. Beob. h. a. u. f. f. a. ph. i. e. n. D. e. l. l. u. a. d. e. r. A. n. d. i. e. r. b. e. i. h. y. p. e. r. t. e. b. e. i. n. i. r. k. r. a. n. k. n. c. h. w. a. n. g. s. c. h. a. f. t. 42 1023-1027 1921.

^{189f}Hilfmann H. Haupt W. Über die Capillaroscopia während der Schwangerschaft. Zbl. f. Gynäk. 45 10 19 1920.

sign if the stases do not completely disappear on changing from the upright to the horizontal position¹⁶⁸⁶ In edema and with high sedimentation rates stases are pronounced In hydramnion a tortuous appearance of the capillary loops has been noticed¹⁶⁸⁹ It should be emphasized that stases of course are not a symptom of pregnancy They are the expression of an impaired peripheral circulation and occur in many conditions The number of capillary loops increases in two thirds of the pregnant women after the second month but not infrequently only as late as in the seventh or eighth month (Vinogradova after Melbard¹⁶⁹⁰)

Two months after delivery the normal number of hair pin type capillary loops is usually found again

The high permeability of the capillary wall is shown by the fact that the tourniquet test is positive in 80 per cent of the pregnant women¹⁶⁹¹ The serum of blisters produced by cantharides on the skin of pregnant women contains three to four times more lymphocytes than under normal conditions This observation can be interpreted as evidence of the higher endothelial permeability¹⁶⁹¹ Other studies of cantharides reactions¹⁶⁹² showed opposite conclusions

Pregnancy is by far the most frequent cause of varicose veins in women Only about 3 per cent of the women patients of a large varicose vein clinic had their trouble before their first pregnancy¹⁶⁹³ The incidence figures given by a number of authors vary within wide limits but 50 per cent does not seem too high They most often involve the lower legs only with a preference for the right side In almost 20 per cent of the pregnant varicosities of the vulva may produce large bluish tumorlike convolutions

Hemorrhoids are almost as common as varicose veins of the vulva

The most simple explanation of the varicosities of pregnancy is the pressure of the uterus on the large pelvic veins However this cannot be the only cause since varicose veins sometimes develop in an early stage of pregnancy when pressure is negligible They sometimes appear as an early symptom of pregnancy soon after the first missed menstruation (Balard and Mehon after Vignes¹⁶⁹⁴) Even at the common time of appearance in the third month the pressure of the uterus does not give a very plausible explanation since uteri of equal size with tumor hardly cause varicose veins Other observations¹⁶⁹⁵ can be interpreted against the purely mechanical pathogenesis The varicose veins of pregnancy often appear in crops and the temperature over newly developed varicosities is up to four centigrades higher than over older ones and over the symmetrical skin¹⁶⁹⁴ It is interesting that large intra abdominal tumors may cause edema but rarely varicose veins The elastic fibers in the wall of the varicose

¹⁶⁸⁶ H. M. Graviditätsdermatosen. Endokrinologie 17: 341-394, 1936

¹⁶⁸⁷ H. M. M. Valur d'au tique d la capillaroscopie dans la grossesse et dans la période postnatale. Gynéc. Obstet. 37: 60-69, 1934

¹⁶⁸⁸ S. G. H. Cantharidenreaktion u d Schwang schaft. Monatsschr. f. Geburt u. Gynäk. 78: 47-53, 1934

¹⁶⁸⁹ J. L. W. F. a d Lash. A. F. Permeabilité des capillaires cutanés pendant la gestation. Arch. Int. Med. 39: 1-14, 1937

¹⁶⁹⁰ M. Daurand. A. M. Varicose veins in pregnancy. West. J. Surg. 47: 81-94, 1939

¹⁶⁹¹ H. M. A. V. rissen und Schwang schaft. Med. Klin. 17: 13-7, 1921

The outbreak of the disease is often preceded by premonitory itching without visible changes other than a few wheals. Often in this prodromal period nausea, headache, and fever may be observed but lack of uniformity characterizes this phase just as much as the later stages. The rash hardly ever breaks out on large surfaces. Usually in one or a few areas, e.g., around the navel and on some parts of the arms erythematous patches appear which lead to the fully developed syndrome. Wheals, prurigo-like small papules, vesicles, pustules, groups of blisters and bullae appear in crops and create a rather polymorphic picture. While at times erythematous and urticarial lesions predominate, in other periods the abundant bullae may present a pemphigus-like aspect. In some cases aggregated scratched small papules on the trunk and on the extremities resemble prurigo Hebra. This dermatosis has been described as a separate dermatosis under the name of prurigo gestationis¹⁷⁰. It is probably only a variety of the highly polymorphic herpes gestationis^{170a}. Everybody who has observed cases of dermatitis herpetiformis over a long time knows that such prurigo-like stages occur. However, the separation of prurigo gestationis from herpes gestationis is still stressed by some authors¹⁶⁶.

The erythematous and vesicular patches of herpes gestationis often spread centrifugally leaving annular or gyrate lesions with accentuated edges and red scaly or pigmented centers. There is little tendency to involve the mucosae. Ulceration does not occur and no scars develop unless severe pyogenic infection complicates the course. Besides the discomfort of large oozing surfaces, in some cases the main complaint of the patients is the furious itching, burning, stinging or pain which accompanies the crops. The attacks of pruritus in particular which can be provoked by various causes, especially psychic excitement, can make the condition of the gravid woman a most miserable one. It needs all the efforts of dermatological and psychological treatment and in particular the assurance of complete recovery without disfigurement to keep up the morale of the patient.

The eruption affects the extremities more often than other regions but no part of the body surface is sure to remain free. The nailbeds may become infected and the nails may be shed. The outstanding histological feature is the eosinophilia in the blister serum and in the tissue, particularly in perivascular infiltrations. Blood eosinophilia is common too. Eosinophilia especially in the tissue, though not being specific, frequently accompanies allergic diseases and therefore suggests an allergic nature of the dermatosis¹⁶⁹. The recession of the blood eosinophilia is considered a favorable prognostic sign^{170a}.

The relationship to pregnancy is of course an outstanding characteristic of the disease. Though occasionally an early symptom of pregnancy, herpes gestationis has been seen to appear most often in the second half of pregnancy¹⁷². If there are attacks in subsequent pregnancies the onset may be earlier each time.

¹⁷⁰Heanl r J Sur la question du prurigo 3rd Int. nat. Congr. of Dermat. Ed. don 1896

^{170a}Rieck H. Herpes gestationis. Handb. d. H. u. Gk. 7. 637-651 1931

¹⁷²Filisch G. O. Sur la valeur de l'éosinophilie dans les dermatoses bulleuses et spécialement dans la dermatite herpétiforme de Duhring. Wang 2 1-3 1925

and the disease may become more severe^{1702 1705 1707}. Besides this most common type other relations to gestation occur. Some pregnancies may remain free and only in a later pregnancy will the first eruption occur (Puente Gross in discussion to Rostenberg¹⁷⁰⁸). A normal pregnancy may be had between pregnancies with herpes gestationis¹⁷⁰⁹. The onset may be very late in the last days of pregnancy¹⁷⁰⁸ or even in the puerperium. The disease may break out during pregnancy improve or heal with the approaching delivery and then be followed by a severe crop during the puerperium¹⁷¹⁰. Characteristically herpes gestationis does not remain after pregnancy as an ordinary dermatitis herpetiformis. In a few cases menstrual recurrences have been observed^{1711 1712}. So far unique is the case of herpes gestationis caused by choriocarcinoma two years after a pregnancy with hydatidiform mole¹⁷¹³.

The prognosis is favorable for the mother. A fatal outcome is rare and may be caused by sepsis rather than by the dermatosis itself (Schonfeld after Riecke^{1703 1707 1714 1715}).

The prognosis for the child is unfavorable. Stillbirth ends about fifty per cent of the pregnancies complicated by herpes gestationis¹⁷⁰⁶. Babies born alive died in several instances from infection during the first year^{1704 1716}. Skin lesions in the living or dead child possibly pertaining to the dermatosis of the mother have been reported^{1717 1718 1719} but the evidence of true congenital herpes gestationis is not convincing¹⁷⁰⁹.

The etiology and pathogenesis of herpes gestationis is not much better understood than that of dermatitis herpetiformis. It is just the connection with pregnancy which suggests some explanation. Toxemia of pregnancy with damage to the liver to the kidneys and to the skin has often been accused. The nitrogen content of the urine is reduced during the eruption and increases with recovery. Just as in dermatitis herpetiformis eruptions may be precipitated by internal or percutaneous application of potassium iodide (Jadassohn's test). However this phenomenon is not constant. Endocrine secretions may as in the case of impetigo herpetiformis provide a better explanation than those given today. Rostenberg¹⁷⁰⁸ in his case found the anterior pituitary like principle increased in the urine twenty six days after delivery. In Elliott's¹⁷¹² case of herpes gestationis caused by choriocarcinoma the pregnancy tests were strongly

¹⁷⁰²Heckert E. Ein Fall von Herpes gestationis mit tödlichem Verlauf. *Geneesk. Tijdschr. v. Ned. d. Ind.* 68: 1094 1095 19 8. *Zbl.* 31: 57.

¹⁷⁰³Howard R. Herpes Gestationis. *Arch. Dermat. & Syph.* 28: 78. 1913.

¹⁷⁰⁴Madd n J F. Herpes gestationis. *Arch. Dermat. & Syph.* 32: 550. 1935.

¹⁷⁰⁵Rostenberg R. Herpes gestationis. *Arch. Dermat. & Syph.* 30: 736. 1934.

¹⁷⁰⁶Archel F. Contributo allo studio dell'herpes gestationis. *Glor. Ital. di dermat. e sif.* 73: 1353. 13 2 1935.

¹⁷⁰⁷Lur J J and Bonfigli H H. Polymorph Schwangerschafts dermatitis. *Rev. argent. de dermat. e sif.* 15: 211. 1937. *Zbl.* 42: 475.

¹⁷⁰⁸Tommassi L. Contributo alla conoscenza dell'herpes gestationis. *Glor. Ital. d. mal. ven.* 34: 44. 1934.

¹⁷⁰⁹Crosi A. Herpes gestationis e dermatitis polymorpha dolorosa (Dühring Brocq). *Glor. Ital. di dermat.* 73: 15. 174. 1937. *Zbl.* 42: 85.

¹⁷¹⁰Elliott J A. Eruptions Dermatoses of Toxic Origin. Case Involving an Association With Choriocarcinoma. *Arch. Dermat. & Syph.* 37: 219 233. 1934.

¹⁷¹¹Obafima W. Ein Fall von Herpes gestationis. *Jap. J. Dermat. & Urol.* 23: 43. 1933. *Zbl.* 45: 701.

¹⁷¹²Geilhorn H. Eczema in Pregnancy. *Am. J. Obst. & Gynec.* 28: 409. 1933.

positive. The relationship of dermatitis herpetiformis to ovarian function however inconstant and contradictory it may be cannot be easily dismissed in view of the considerable case literature.¹⁷⁰⁸ However there still is no satisfactory endocrine explanation. Some evidence points to allergy. The repeated occurrence in pregnancies with each subsequent attack starting earlier and taking a more severe course has its parallel in acquired allergy. The urticarial element in the eruption and the marked eosinophilia in the blood blisters and tissues lend support to an allergic hypothesis. Passive transfer has not been successful.¹⁷¹¹ A hormone may well act as an allergen. Tommisi¹⁷¹¹ suggests the corpus luteum such autogenous allergies are known. Infection as a cause can neither be denied nor as yet be proved. Thus the pathogenesis of herpes gestationis is well as that of dermatitis herpetiformis remains unknown.

Based on the hypothesis that herpes gestationis is caused by toxemia and the inability to produce neutralizing antibodies Mayer and Linser¹⁷¹⁰ inaugurated the treatment of herpes gestationis with intravenous injections of 10 to 20 c c of fresh serum of normal pregnant women. With this method Seitz cured 37 out of 38 cases of the various dermatoses of pregnancy. This method is still widely applied. In some countries this serum is available in ampoules. The serum of pregnant mares has been successfully used too. In spite of successes the theoretical foundation of the treatment with normal pregnant women's serum however has become untenable because of the equally successful treatment with normal serum, horse serum and especially with Ringer's solution. Riecke¹⁷⁰² gives the following formula for this mixture:

Sodium chloride	1.8
Calcium chloride	0.048
Iota-um chloride	0.084
Sodium bicarbonate	0.06
Aq. distill. ad	200.0

This solution is injected intramuscularly or subcutaneously in doses of 150 to 200 c c. Similar success has been achieved with serum or blood from the umbilical cord with the patient's own blood¹⁷¹² and with milk. In the published cases one or the other of the above mentioned methods especially the normal pregnant women's serum has helped. One may surely assume however that failures of the therapy have not been reported with the same zeal as the successes. Only a few of the observers have seen a considerable number of cases of this rare disease and the often irregular course of the dermatosis should be remembered in evaluating any method of treatment. Lately contradictory reports on the sulfonamides have appeared.^{1713, 1714} Ovarian extract¹⁷¹⁵ corpus luteum¹⁷⁰⁹ and cortisone¹⁷¹⁶ have also been advocated.

¹⁷⁰⁸ Mayer A. and Linser F. In: *Versuch Schwangerchaftstoxikosen durch Flüssigkeit von Schwangerchaftserum zu heilen*. *Monatsh. f. med. u. Naturgesch.* 87: 737-739, 1910.

¹⁷⁰⁹ Wartin J. *Dermatite polymorphe localisées à autohémothérapie*. Bull. Soc. fran. d. dermat. et syph. 21: 41-44.

¹⁷¹⁰ Turner C. J. and Zak R. J. *Herpes Gestationis*. Am. J. Obst. & Gynec. 81: 5-5-7, 1911.

¹⁷¹¹ Lewis J. M. *Herpes Gestationis: Successful Treatment With Sulf. thiazol*. Arch. Dermat. & Syph. 46: 651-62, 1911.

Purpura—It has already been mentioned that pregnancy increases the permeability of the capillary wall and that the tourniquet test (Rumpel Leede phenomenon) is often positive. Spontaneous petechiae are occasionally seen under the strain of labor. More severe purpuric rashes have been observed¹⁷²⁹ some of them with dangerous hemorrhagic complications. They are generally considered toxic. They disappear after delivery¹⁷³³ but sometimes recur in subsequent pregnancies in some cases in the same spot as a fixed eruption¹⁷¹. Rushmore¹⁷²² has collected forty seven cases mostly of severe purpura in pregnancy. The mortality of the mothers as well as of the children exceeded fifty per cent. Some cases have the character of thrombocytopenic purpura¹⁷¹³. Pregnancy may activate dormant thrombocytopenic purpura or cause the first manifestations of the disease. Besides purpuric skin lesions of great variety in size severe even fatal hemorrhages from the nose the gums and other sites may occur. If treatment fails termination of the pregnancy is indicated. Bruise like hemorrhagic discolorations of the abdominal wall in and about the umbilicus occur in ruptured extrauterine pregnancy and other intra abdominal hemorrhages. This is known as Cullen's sign¹⁷⁷⁴.

Miscellaneous Eruptions—It would be monotonous to describe all the rashes which have been observed in pregnancy other than the well characterized dermatoses. There are morbilliform erythemas sometimes with eczema or with pruriginous papules. Erythema exudativum multiforme^{1725 1714} is also on record. Its differentiation from herpes gestationis is difficult in some cases. Urticaria of pregnancy, angioneurotic edema and lichen urticatus are known. Pruritus of pregnancy is common and sometimes of a severity which may cause abortion¹⁴⁴⁹. Eczema¹⁶¹⁵ lichenoid multiple lesions resembling localized prurigo¹⁷¹⁷ pemphigus vulgaris¹⁷²³ scleroderma^{1729 1730} cutaneous atrophy in spots (Temesvary and Oppenheim after Nova¹⁴⁶¹) and other conditions have occasionally been seen during pregnancy sometimes repeatedly and usually healing after delivery. Seitzky¹⁴⁴⁰ described toxic symmetrical dermatitis. It has been said that the pregnant woman has a marked tendency to develop drug eruptions¹⁷³¹. Pruritus vulvae and vulvitis of pregnancy is often caused by monilia but is rare compared with

¹⁷¹ Hais E K. Seltene Hautveränderungen bei Schwangeren. *Med Klin* 24 933 934 1928

¹⁷¹³ Igles H and Stassanle. Purpura et idivant au cours de trois gestations successives. *Progrès Méd* 46 167 169 1911 Zbl 1 495

¹⁷²² Rushmore S. Purpura Complicating Pregnancy. *Am J Obst & Gynec* 11 553 560 1925

¹⁷²³ Satisfalvy J. Pregnancy Complications—Thrombopenic Purpura. *Ztschr f Geburtsh u Gynäk* 118 65-66 1930

¹⁷²⁴ Cullen T S. Bluish Umbilicus as Diagnostic Sign in Ruptured Extrauterine Pregnancy. *Contributions to Medical and Biological Research etc.* New York 1919 Paul B Hoeber pp 4 0-4 1

¹⁷²⁵ Gross H. Erythema multiforme gestationis. *Arch. Dermat & Syph* 23 567 1931

¹⁷²⁶ Ebert. Toxic Eruption of Pregnancy. Multiform Erythema Type. *Arch. Dermat & Syph* 25 509 510 1927

¹⁷²⁷ Davies J H T. Prurigo annularis. *Brit J Dermat* 63 143 145 1941

¹⁷²⁸ Klopstock. Pemphigus vulgaris Associated With Pregnancy. *Dermat Ztschr* 60 303 1914

¹⁷²⁹ Anselmino I J and Hoffman P. Leber Sclerodermie und Schwangerschaft. *Ztschr f Geburtsh u Gynäk* 103 60-66 1932

¹⁷³⁰ Gard. Case of self-induced moniliae à la suite d'une grossesse. *Troubles ovariens. Le Scalpel* 2 815 1912 Zbl 11 74

¹⁷³¹ Rosenfeld R. Skin During Pregnancy and Puerperium. *Intol & Cutan Rev* 48 86-88 1944

the frequent occurrence of yeasts in the vagina of pregnant women.¹²⁷ The typical monilia vulvitis causes itching and redness of the introitus and of the vagina. Yellow specks of thrush which are not easily removed without bleeding continue the mycelia. Vaginal thrush caused by *Monilia albicans* was found in 25 per cent of 200 consecutive pregnancies having leukorrhoea in Edinburgh Scotland.¹²⁸ It is advisable to look for vaginal thrush in order to safeguard the baby from infection at birth. Very little is known about the cause of the more severe ulcerations of the external genitalia in pregnancy which have occasionally been seen.

Stimulation of Growth—Symmetrical erythema of the palms, mainly on the thenar, hypothenar and finger tip eminences has been described in connection with a variety of internal conditions notible among them being cirrhosis of the liver and pregnancy. The erythema usually leaves the triangle shaped center of the palms pale. The condition is often associated with multiple sometimes pulsating spider like telangiectases.^{129, 130} The erythema as well as the telangiectases often vanishes after parturition. In some cases the spiders result in actual hemangio endothromas which may even become locally malignant and infiltrating.¹³¹

Preexisting and apparently stationary hemangiomas may start to grow during pregnancy.¹³²

Fibroma molluscum gravidarum^{133, 134} is an eruption of small soft pedunculated or sessile sometimes pigmented fibromas which appears in crops during the latter half of pregnancy and disappears after childbirth. The little growths appear especially around the neck and in other areas where skin rubs against skin e.g. under pendulous breasts and in the axillary folds. They may be associated with large brown spots so that a close resemblance with Von Recklinghausen's disease results including the microscopic anatomy. The lesions which appear during pregnancy usually¹³⁵ but not always¹³⁶ disappear after delivery. While the widespread or even universal types of fibromatosis gravidarum as it should be called¹³⁷ are rare, a crop of some cutaneous tags¹³⁸ around the neck is common in pregnancy. Pregnancy stimulates the growth of skin cancer

¹²⁷ Watson F C and Cartwright P W. Significance of Vulvovaginitis in Pregnancy. J A M A 113: 30-31 1915.

¹²⁸ List W C and Crutchshank L C. On Thrush. Special Reference to Vaginal Thrush. Edinburgh M J 47: 463 1910.

¹²⁹ Halperin E. Multiple Telangiectases. Brit J Dermatol 27: 74 1935.

¹³⁰ Walz H F and Becker W. Erythema palmaris and telangiectases. Arch Dermatol & Syph 61: 616 1931.

¹³¹ Richardson H F. Multiple Telangiectases. Brit J Dermatol 27: 74 1935.

¹³² Darrach J. Subcutaneous Hemangiomas. J Obstet & Gynecol Brit Emp 43: 60-61 1934.

¹³³ Lutz J. Fibroma Molluscum Gravidarum. Am J Obstet & Gynecol 52: 191 1936.

¹³⁴ Lutz J. Fibroma Molluscum Gravidarum. Am J Obstet & Gynecol 52: 191 1936.

¹³⁵ Burg F. Multiple Fibromatosis Gravidarum. J Obstet & Gynecol 52: 191 1936.

¹³⁶ Walz H F. Multiple Fibromatosis Gravidarum. J Obstet & Gynecol 52: 191 1936.

¹³⁷ Fischl F. Multiple Fibromatosis Gravidarum. J Obstet & Gynecol 52: 191 1936.

¹³⁸ Ceschwiltz W. Multiple Fibromatosis Gravidarum. J Obstet & Gynecol 52: 191 1936.

¹³⁹ Timpler H J. Cutaneous Tags of the Neck. Arch Dermatol & Syph 33: 405 1936.

produced in rabbits by the application of carcinogenic tar fractions¹⁷⁴ The growth stimulating effect of the estrogens is suggested as a cause The hypercholesteremia of pregnancy makes one expect a rather frequent occurrence of

Fig 216



Fig 217

Fig 16—Fibroma of pregnancy

Fig 1 Fibromas (skin tags) of pregnancy These little tumors may appear early in pregnancy and some may reach larger size

lipoidoses It is surprising that xanthoma and xanthelasma in connection with pregnancy is rare (author's case see also Schaaf¹⁶¹⁸) Growth stimulation may also be the cause of the so called gingivitis hypertrophica of pregnancy This

¹⁷⁴ Krotkina N. Lebens Einfluss von Cravidität und Lactation auf die durch Teerpinlu generated Epithelwachstum am Kinnchnehr Zisch. Forsch 22 450-457 1944

disorder^{1745 1747} frequently starts in the third month. In the early stages the gums are red and bleed easily. Then they swell especially at the margin. The bulging edge may develop folds which cover the teeth and cause considerable trouble. If this hypertrophic stage is restricted to a small area an epulis like nodule may result. The term epulis gravidarum which has been used is misleading because of the different character of the two conditions. However true epulis occasionally starts in pregnancy and the growth of a preexisting epulis (Seitz) or giant cell sarcoma¹⁷⁴⁷ may be stimulated. The swelling of the gums disappears quickly after delivery, sometimes within a week. Gingivitis hypertrophica of some degree is seen in more than half of all pregnant women. In 32 per cent the condition was moderately severe and in 4 per cent severe.¹⁷⁴⁸ These figures were observed in Germany and may well differ from those of other countries.



Fig. 918 — Xanthoma stated in pregnancy

This gingivitis of pregnancy is primarily a connective tissue hypertrophy. The inflammation seems to be secondary although it may dominate in the fully developed case. It has been shown that similar hypertrophy of the gums can be produced in monkeys by injection of the concentrated urine of pregnant women.¹⁷⁴⁹ Huber¹⁷⁵⁰ found a high level (700 M U) of follicular hormone in one liter of urine of a twelve year-old boy who suffered from hypertrophy of the gums. Newborn children often show a comparable succulence of the oral mucosa which disappears within a few days leaving the empty sucking folds. This may be one of the effects of the maternal or placental hormones. Vitamin C deficiency and hypocalcemia are accused by other mostly European dentists of being the main cause of gingivitis in pregnancy. The proponents of this theory base their opinion on the low content of vitamin C in the serum of pregnant

- ¹⁷⁴⁵Fortier J. Gingivitis in Pregnancy. *Union méd du Canada* 63: 45-46 1936
¹⁷⁴⁶Monash G. Proliferative Gingivitis of Pregnancy. *Cases Arch Dermat & Syph* 21: 520-526 1931
¹⁷⁴⁷Wachuck J. Schwangerschaftsgingivitis und ihre Behandlung mit A. B. und Vitamin C. *Arch f Gynäk* 169: 571-578 1939
¹⁷⁴⁸Ziskin B. Blackberg G. and Stout A. E. Tb. Gingivitis During Pregnancy. *Surg Gynec & Obst* 57: 719-76 1953
¹⁷⁴⁹Huber H. Zahnfleischwucherungen in der Schwangerschaft. *Zbl f Gynäk* 88: 1977-1991 1935

women suffering from gingivitis compared with normal controls and on the therapeutic effect of vitamin C.

Many dentists advise treatment with Vitamin C and calcium. It is claimed to be helpful if the process is not too far advanced.^{1748, 1751} The teeth should be cleaned, checked and treated at the beginning of pregnancy in order to minimize secondary infection. Only complications require local treatment.

The treatment of the dermatoses of pregnancy is both topic and systemic. The former is determined by the type and stage of the lesion. In the vast majority



Fig. 210. Severe eruption in pregnancy. There was almost no acne present before.

of the cases it is possible to keep the patient comfortable or to heal the eruption even during pregnancy. In the more severe and of course the dangerous cases the treatment should follow the methods described under herpes gestationis. Ringer's solution should always be tried first since it is not connected with any risk. Its antipruritic effect has been praised.^{1, 22} Injection of 1 to 5 c.c. of the

²² Brauer R. Pregnancy Complications. *Gingivitis Med Klin* 28: 280-81 1939.

¹ Sela S. L. and C. H. Gold. *Am J Obstet Gynecol* 2: 161-165 1937; 21: 58-64 1939.

patient's own blood has also been recommended.¹⁷⁵³ The serum of normal pregnant women should be given if Ringer's solution fails. In these cases the question of the artificial termination of the pregnancy will arise. In herpes gestationis the prognosis is favorable for the mother and less so for the child. These cases will rarely require the termination of the pregnancy. If the diagnosis of impetigo herpetiformis is made the pregnancy should be interrupted as soon as possible before large areas become involved and infected and make the operation dangerous.¹ Even early abortion does not secure an absolutely favorable prognosis.¹⁷⁵⁴

Influence of Pregnancy on Existing Dermatoses—Pregnancy often influences the course of existing dermatoses. The observations regarding *psoriasis* are contradictory but improvement during pregnancy occurs quite often. The same is said of *acne* (Kaufmann in discussion to Seitz¹⁶²⁷) but here too the observations are conflicting.¹⁶³⁰ The author has seen at least two cases of *acne conglobata* with severe exacerbations during pregnancy.

In several strikingly parallel instances patients with *alopecia areata totalis* regained their hair during pregnancy only to lose it again a short time later.¹⁴ Seborrheic alopecia usually improves or is arrested.

Some contrasting observations on scleroderma and pregnancy have appeared (Jadassohn in Wiener¹⁴ 3: 16-5 1889 17-9). (See scleroderma.)

Von Recklinghausen's disease often takes a turn for the worse in pregnant women.¹⁷⁵⁴

¹⁷⁵³Lysander A.: Behandling af de Schwangerschafts Dermatoser. Svenska läk. tidn. 8: 31-33 30 1934 Zbl. 49: 151.

¹⁷⁵⁴Sharpe J. G. and Young R. H.: Neurofibromatosis. Effect of Pregnancy on the Skin Manifestations. J. A. M. A. 106: 682-693 1936.

CHAPTER XXIV

CHILDBIRTH AND PUERPERIUM THE SKIN IN THE NEWBORN

Childbirth and Puerperium

Emphysema—In rare instances the intrathoracic pressure caused by the labor pains can puncture the lung tissue and press the air under the visceral pleura along the mediastinal spaces to the neck. Once such an air channel is formed more and more air is pumped into the loose connective tissue. Finally the subcutaneous tissue becomes inflated and painful and gives the palpating finger the crepitant sensation found in some chest injuries and in gas gangrene. The first symptoms of subcutaneous emphysema are most frequently found in the face less often in the nape of the neck or above the sternum¹⁷⁵. Some authors feel that the phenomenon is better explained by rupture of the tracheal wall due to the intense vibration caused by screaming. Pleural adhesions are also believed to play a part^{175 177}. Only very rarely has an actual laceration of lung tissue been verified at autopsy (Depaul after Scheuer¹⁷⁶). Even laceration of the buccal mucosa with ensuing emphysema has been observed^{175 178}. The clinical picture of the frog like inflated neck from where the emphysema may travel long distances under the skin must be impressive but even very experienced obstetricians have encountered it extremely seldom about once in several thousand confinements. The patients were almost exclusively primiparae with pelvic contraction and very large babies. The prognosis of the emphysema per se is usually favorable.

Petechiae—Since pregnancy creates a purpuric tendency it is not surprising that under the strain of labor petechiae appear. They are most often seen in the conjunctivae and on the neck and shoulders rarely over the entire body^{187 188}.

Urticaria—Urticaria beginning with labor and disappearing two days later has been seen*.

Pruritus¹⁷⁵⁹ and *Herpes* occur occasionally in the first day of the puerperium

J. Jadassohn personal communication (also author's case)

¹ Kosmak G. W. Cutaneous Emphysema During Labor. Bull. New York Lying-in Hospital 1907 Abstr. Zbl. f. Gynäk. 32 10 4 1909

² Brindley D. Cervicothoracic Subcutaneous Emphysema. Cas. Rev. de gynec. et obstet. 2 19 195 191

³ Stockel W. Tratado de Obstet. 2 Vol. I p. 707 1932

⁴ Matulis J. B. and Martin H. F. Traumatic Purpura Occurring During Labor. J. Obst. & Gynec. Brit. Emp. 40 30-304 1933

⁵ Simunich W. A. Postnatal Complaints in 1000 Consecutive Cases. Illinois M. J. 74 546-551 1934

Nail, Hair—Not all the dermadromes of labor become immediately apparent. The great event leaves its mark on the growing tissues of the nails and hair, but it is only considerably later that these sequelae become evident. From twenty-one to forty-two days after the delivery transverse grooves or lines, very rarely only white stripes, may appear on the proximal ends of all fingernails or on some symmetric nails. These lines, which are known as *Beau's lines*, are more pronounced on the nail of the thumbs and the first fingers than on the smaller



Fig. 220



Fig. 221

Fig. 220—Hoof of an old cow showing periodical line formation. (Courtesy University of Wisconsin, Department of Dairy Husbandry.)

Fig. 221—Horn of an old cow. Physiological ring formation in regular intervals, except on the free end which represents the oldest part of the horn formed during the first years of life. The rings become less distinct the older they are. (Courtesy University of Wisconsin, Department of Dairy Husbandry.)

fingers. They are not always present but they are quite common. They may occur after any acute disease and after gastrointestinal, cardiac and other attacks. Therefore they alone cannot be regarded as a certain indication of preceding childbirth. Since it takes about thirty days for the nail to appear under the edge of the cuticle and since the nail grows about 0.1 mm a day, it seems easy to calculate retrospectively the day of delivery. But individual differences in the rate of growth and other factors make a more accurate determination than the week of the event impossible.⁴³

Beau's lines also appear on the nails of the newborn (see newborn). Comparable to *Beau's lines* of the human nails, ring formation on the horns of cows

after calving are commonly observed and used as an indication of age. Similar marks are known to occur on the hooves of mares.*

The growing hair is affected by the trauma of childbirth just as is the nail. A considerable number of hairs are so weakened that they fall out after two to three months. Other hairs show only a thinned portion of varying length (Pohl Pinkus mark). If the puerperium is complicated by fever and infection the mark may involve a longer stretch. This mark is not only thinner but also lighter in color. Considering the daily rate of the head hair growth as 0.3 — 0.5 millimeter or approximately 1 cm. per month¹⁴⁸ it is possible to determine the day of the delivery within certain limits. If several pregnancies follow each other closely the hair does not have enough time to recover and stays thin and short. Some veterinarians believe that animals who are prevented from eating the placenta lose much hair¹⁴⁹ even to the degree of complete epilation. Gross advises administration of 5 gm. of placental extract three times daily for the treatment of post partum hair loss in women. His series of 24 patients afflicted with this condition which offers a good prognosis anyway needs confirmation on a larger scale.

Skin irritations from the lochia and dermatitis around the nipples shall be mentioned for the sake of completeness. Simunich noted in one thousand consecutive cases the following postnatal complaints concerning the skin: five cases complained of pruritus, four of which involved the extremities only, one the vulva. There were four cases of excessive perspiration and four cases of herpes between the second and seventh days. In seven cases the axillary glands were swollen. Reports of infections of many kinds¹⁵⁰ and onset of chronic diseases are numerous but no characteristic dermatoses seem to have been described in relation to this phase. Puerperal sepsis may exhibit itself in erythematous, morbilliform, scarlatiniform and other rashes. Exfoliative dermatitis probably caused by *Staphylococcus aureus hemolyticus* has been seen.¹⁵¹ Purpura occurred also in the course of puerperal complications. Sensitization of a woman to her own milk with allergic symptoms like urticaria and angioneurotic edema is considered possible though still lacking confirmation.¹⁵²

The dermatoses of pregnancy usually subside in the postnatal period but *exacerbations in the early puerperium* are especially characteristic of herpes gestationis.

There are two types of ring formation on the horns of cattle. Normally rings appear at the base of the horn in both sexes very early after the third year. It seems that they are caused by seasonal change of food. Besides this physiological ring formation any event which depresses the metabolism of the animal deep enough may leave its mark on the growing horn. Such events may include dietary nutritional change and also pathological births. The normal births do not seem to cause rings. Analogous phenomena are important in the hair of sheep. Subnutritive nutrition causes thinning of the hair even to such an extent that the hair breaks off and the fleece may become lost. (Personal communication from Prof. E. H. Re, Department of Dairy Husbandry, University of Wisconsin.) (See also J. H. R. 1930)

¹⁴⁸ H. H. R. J. *Birds and Mammals*, Handb. d. H. u. Gk. 14, 1, 19-217, 1930.

¹⁴⁹ Gross, F. R. *Dermatology in Relation to Endocrinology*, Clinica 2, 813-833, 1944.

¹⁵⁰ Lee, J. B. *The Principles and Practice of Obstetrics*, ed. 7, Philadelphia and London 1934.

W. B. Saunders Co.

¹⁵¹ Rindler, A. *Exfoliative Dermatitis Due to Staphylococcus Aureus Hemolyticus During Puerperium*, Zbl. f. Gynäk. u. Gynäk. 63, 371-372, 1939.

¹⁵² Duke, W. W. *Allergic Asthma, Hay Fever, Urticaria and Allied Manifestations of P. Asthma*, St. Louis 1923, The C. V. Mosby Co.

These figures were obtained from 250 measurements. Heller is skeptical about the practical value of these measurements since individual variations are common.

On the borderline of physiological and pathological peculiarities are the milium of the face, the symphysis praeputialis which disappears by desquamation, the mongol spots, and the superficial epithelial cysts in the midline of the hard palate.¹⁷⁷ Several types of flat and faintly red telangiectases are known as nevi pallidi (stork bites). Unna's nevus is a relatively inconspicuous macular purplish irregularly contoured telangiectasis of the nape of the neck. Other similar vascular maculae occur on the forehead,^{177a} on the eyelids and elsewhere. Most of these vascular nevi disappear spontaneously. They should not be confused with true hemangiomas. Icterus neonatorum of varying degree occurs in about two out of three babies and clears up during the first week. A peculiarity of the infantile skin is its tendency to form blisters. Thus scabies in early childhood, syphilis, and even psoriasis may produce large blebs, and the urticaria of this age often shows a central vesicle and a papular appearance giving it the characteristics of strophulus. The allergic skin reactions are likely to be vigorous or even violent so that a mild test reaction, e.g., a moderately positive Pirquet, should be judged with great caution.¹⁷⁸ Of great importance is the hemorrhagic tendency in the newborn. In 66 per cent of the babies the endothelial permeability, as measured by the number of petechiae elicited under controlled conditions by the application of a suction cup, is increased above the adult level. At the age of ten years this physiological hemorrhagic tendency has disappeared.^{177a}

The incidence of the more severe *hemorrhagic diathesis of the newborn* is about one in two hundred.^{177b} with a marked predisposition by asphyxia at birth. The disease is not noticeable at birth. On the third day symptoms of hemorrhagic disease, such as the oozing of blood from the navel, from circumcision, and from other wounds or bruises, may become manifest. There are often large purpuric spots, but according to Quick,¹⁸⁰ petechiae are characteristically absent. Melena neonatorum is the most common type of the disease. This trouble is due to hypoprothrombinemia. The prothrombin level at birth is near the adult level, but it may fall during the first few days to as low as 10 per cent. It returns to normal at the end of the first week.¹⁸⁰ The cause of this drop is a deficiency in vitamin K. The human body is unable to synthesize vitamin K, which comes entirely from plants. The newborn is physiologically provided with enough vitamin K from the mother to tide him over the first week, until he can draw from the harvest of his intestinal flora, which becomes established during this time. If the baby does not get enough maternal vitamin K, or if his allotment is used up or destroyed before his own is ready for use, the level falls below

¹⁷⁷Mayerhofer, E. Hautreaktion an der Neugeborenen Lippen vje. 85: 402-407, 1933. Zbl. 46: 755.

^{177a}Hagenbuch, M. Ueber Telangiectasen bei Neugeborenen. Ztschr. f. Geburt u. Gynäk. 89: 127-133, 1915.

^{177b}Hay, F. W. Beitrag zur hämorrhagischen Erkrankung des Neugeborenen. Die Rolle der Endothelasthenie. Jahrb. f. Kinderh. 123: 222-234, 1931.

¹⁸⁰Quick, F. L. Hemorrhagic Disease of the Newborn. 354 Cases. J. Pediat. 10: 1, 1931.

the critical point and causes hypoprothrombinemia and hemorrhage. Vitamin K restores the bleeding mechanism to normal. If 2 mg of vitamin K (menadiolone) are given to the mother within two days before delivery, the baby's vitamin K ration is increased enough to prevent hemorrhagic disease.¹⁷⁷⁸ The modern treatment of hemorrhagic disease of the newborn has reduced the mortality from 57 per cent to 20 per cent.¹⁷⁷⁸

A group of phenomena in the skin of the newborn is explained by the effect of maternal or placental hormones. The squamous epithelium of the vagina of newborn girls develops a marked hyperplasia and becomes piled up to a thickness of 30-40 layers with the top layer constantly desquamating.^{1777, 1780} The vaginal smear shows an abundance of nucleated squamous cells with pyknotic nuclei indistinguishable from the smear of pregnant women. This phenomenon is clinically noticeable as a creamy white discharge rarely mixed with blood from the cervix. A few days after birth regression of the hyperplastic epithelium sets in and the normal infantile vaginal mucosa develops. This phenomenon is so regularly found and so striking that it has been suggested to make use of it for the objective determination of the age of a newborn baby.¹⁷⁷⁷

Not so constant as the reaction of the vaginal epithelium but well known for ages is the swelling and secretion of the mammary glands in the newborn of both sexes (witch milk). The *linea alba*, especially between the navel and mons veneris, becomes pigmented in 8 per cent of the babies.¹⁷⁸¹ This pigmentation becomes visible at the age of three weeks and persists two to three months. The succulence and sometimes even the swelling and fold formation of the gums in newborns (suckling folds) has been compared to the hypertrophic gingivitis of pregnant women¹⁷⁷⁸ (see pregnancy). The *labia majora* and also the male genitals of the newborn are often swollen and succulent. This also may be due to hormonal influence. Other influences of pregnancy have been observed in the internal genitals of male and female newborns.¹⁷⁷⁸

The comedones and the false milk are the enlarged sebaceous glands and the sometimes observed acne of the newborn (also his vigorous lanugo growth) have often been interpreted as hormonal pregnancy reaction. One has even in view of the numerous gonadal stimulations spoken of a miniature puberty of the newborn. The hypertrichosis of the newborn has also been called a parallel to the hypertrichosis of pregnancy.^{1481, 1782}

¹⁷⁷⁸Dust H R. The Fat Soluble Vitamins. Handbook of Nutrition. Chicago 1943. American Medical Association.

¹⁷⁷⁹Fraenkel L and Ispanicolasou O N. Growth, Desquamation and Evolution of the Vaginal Epithelium of Female Infants. With a Consideration of the Related Hormonal Factors. *Am J Anat* 62: 477 1934.

¹⁷⁸⁰Philipp F. Schwangerschafts- und ungeborenen Vaginalismus. *Wien Klin Wochenschr* 17: 797 800 1934.

¹⁷⁸¹Neumann H O. Histologisch und experimentell Untersuchungen zur Frage der Schwangerschaftsreaktion der weiblichen Genitalien. *Ztschr f Gynäk u Gynäk* 99: 100-135 1910.

¹⁷⁸²Neumann H O. Schwangerschaftsreaktion der weiblichen Genitalien. *Sitzungsber d Gesellschaft d B f r d g Naturw zu Marburg* 65: 61 190 1911.

¹⁷⁸³Eppel B. Über die Schwangerschaftsreaktion der weiblichen Genitalien. *Acta paediat* 11: 100-106 115 121 1930.

¹⁷⁸⁴Leber C. Hautkrankheiten im Säuglingsalt. *Handb d H u Gk* 18: 450-557 1930.

CHAPTER XXV

MENOPAUSE

The known physiological changes connected with the menopause are manifold. The irregularity and the final ceasing of menstruation is due to ovarian changes which may precede the actual menopause for a considerable time. Failure of the formation of corpora lutea and simultaneous persistence of Graafian follicles is thought to be responsible for a temporary oversupply of estrin which may account for menopausal hemorrhage.¹⁷⁸³ The waning function of the ovaries is followed by excessive and persistent oversecretion and excretion of the luteinizing and follicle stimulating factors of the prepituitary.¹⁷⁸⁴ This amount of anterior pituitary hormone which exceeds that in pregnancy by a wide margin disappears only slowly.¹⁷⁸⁵ Injection of large doses of estrogen makes the gonadotropic factor temporarily disappear from blood and urine. In more than 50 per cent of the menopausal women as well as in castrates considerable quantities of the estrogenic factor circulate in the blood and are excreted in the urine.¹⁷⁸⁴ Along with the hormonal changes appear a great number of symptoms: nervousness, exhaustion, headache, insomnia, depression, arthralgia, cardiac consciousness and obesity.

Dermadromes — Hot Flashes and Perspiration: Formication — In the skin hot flashes and excessive perspiration are the most common physiological phenomena of the change of life. In evaluations of large series of the menopausal syndrome^{1783 1786 1787} the incidence of hot flashes varies from 59 to 95 per cent. This is understandable since the phenomenon is extremely variable in severity. In the typical fully developed spell the patient often after an abdominal aura suddenly suffers from a sensation of heat which is described as creeping from the lower parts of the body to the head. The face is usually flushed. In severe attacks the patient has the urge to open her dress and seek an open window in order to satisfy the sensation of air hunger. After a short period of about twenty seconds to three minutes the attack ends with a profuse perspiration which often causes chills. Fortunately such severe seizures are relatively infrequent and the vast majority of women experience only milder flushes. The number of attacks varies from a dozen times a day for several years to a few attacks which almost pass unobserved. The flushes (also called flashes) seem to be a most dependable indication of the cessation of normal ovarian function. In many

¹⁷⁸³Lewis T H Symposium Menopausal Disorders Rev M Progr pp 85-87 1940

¹⁷⁸⁴Frank R T Goldberger M A and Salmon U J The Menopause Symptoms Hormonal Status and Treatment New York State J Med 36 19 1936

¹⁷⁸⁵von Haam E Laboratory Diagnosis of Menopausal and Climacteric States Rev M Progr pp 90-9 1940

¹⁷⁸⁶Hawkinson L F Menopausal Syndrome 1000 Consecutive Patients Treated With Estrogen J A M A 111 390-393 1938

¹⁷⁸⁷McDowell J B and Materson A S Physical and Psychological Symptoms of the Menopause J Obst & Gynecol Brit Emp 47 319-3 6 1940

cases in which deep X ray therapy was directed to still functioning ovaries mostly because of pelvic malignancy, the author hardly ever observed the onset of the induced menopause without flushes. On the other hand if flushes failed to be noticed the sterilization was usually not accomplished. Reynolds showed that the menopausal flush is caused by arteriolar dilatation. He demonstrated in plethysmographic tests that the injection of estrogen in menopausal women is followed by a plateau type of vasodilatation. This reaction does not cause any sensation. While the plateau type response is developing a sharp increase in the tested finger volume may occur and last from three to fifteen minutes. During this flush type reaction the skin temperature is elevated and the patient has a sensation of heat. Excessive perspiration and formication is a complaint in about one third of the cases.¹⁷⁸⁶

Hypertrichosis—While flushes and perspiration have a physiological character a great number of dermatoses have been related to the menopause. On the borderline between physiological and pathological dermadromes is



Fig. 7. Climacteric hypertrichosis.

the hair growth which sometimes appears as a more marked lanugo on the upper lip and sometimes as more or less numerous thick dark bristles on the chin and in the ears. At the same time the hair on the scalp as well as the axillary and pubic hair loses much of its vigor and becomes scanty and thin. In rare cases the menopausal hair growth may assume the character of a true beard which embarrasses the unfortunate woman to an extreme degree. The menopausal

facial hair growth shows a remarkable similarity to the scattered beard of the male castrates. It seems that the functioning ovary affords a certain protection against the hair growth stimulating effect of the adrenals. In two cases of the literature menopausal facial hair growth was strongly stimulated by ovariectomy. In one of these remarkable cases the patient had to shave twice daily and in the other the woman made the best of her condition by exhibiting herself as a bearded woman in the side show of a circus.¹⁷⁸⁵ Rosenhagen tried to solve the pathogenesis of the menopausal beard by paying special attention to this question during autopsies on women above the age of thirty. In thirty cases with marked beard growth the ovaries and adrenals were separated from fat weighed and histologically examined. In five cases adenomas of the adrenal cortex were found but the remaining twenty five did not yield any tangible findings. Perhaps the shift in the relation between the still vigorous adrenals and the atrophying ovaries suggests an explanation.¹⁷⁸⁹ But if so why does not the menopausal hypertrichosis appear more frequently? Another suggested cause is the elevated prolactin level in the blood and urine which together with hypertrichosis is also found in the basophile adenoma of the anterior pituitary.

Pigmentation Benign Cutaneous Neoplasms—Changes in the pigmentation and chloasma resembling spots as well as depigmentations occur quite frequently.¹⁷⁹¹

Stimulation of the growth of small soft cutaneous fibromas and moles is common. It may be explained by the oversupply of prolactin. Similar phenomena can be observed in pregnant women. The so called cutaneous tags or small fibromata pendula around the neck are very common in menopausal and especially obese women.

Obesity—The panniculus adiposus is very often increased. Careful study of the blood chemistry, basal metabolism etc. has so far failed to find the cause.¹⁷⁹² Some women become thinner with the change of life.

Pruritus Vulvae Leukoplakia Kraurosis—Pruritus vulvae is common in the menopause. There are many causes or combinations of causes which may lead to pruritus and its related conditions. The most common irritations those caused by discharge and infected urine¹⁷⁹³ do not strictly fall into the scope of this book. Ovarianitis does not seem to play a major role in vulvar pruritus of the menopause but mycotic infection is very common in America in contrast to Europe.

Latent diabetes with or without sugar in the urine often causes pruritus vulvae.¹⁷⁹⁴ Coincidence with the menopausal age may often cause the physician

¹⁷⁸⁵Kovacs F. Beitrag zur Pathologie des Hirsutismus und Virilismus. Monat. für Geburtsh. u. Gynäk. III 65-70 1932.

¹⁷⁸⁶Bühling R. W. Klimakterische Gesichtshaarung und endokrin. Drüs. = Ztschr. f. d. gew. Anat. Abt. 2 Ztschr. f. Konstitution. I 10 417-433 1934.

¹⁷⁸⁷Bühling R. W. B. Zu Frage der Gesichtshaarung bei Frauen. Ztschr. f. d. gew. Anat. Abt. 2 Ztschr. f. Konstitution. III 193 214 1936.

¹⁷⁸⁸Naegele and Fell. M. Haut und Klimakterium. Endokrinologi. S. 121 1931.

¹⁷⁸⁹A. A. T. et al. Pruritus Vulvae. Brit. J. Derm. 52 3 1 335 1940.

¹⁷⁹⁰Win. L. H. A. d. Strakosch F. A. Vulvar Pruritus as Possible Early Symptom of Unrecognized Diabetes. Journal Lancet 60 537-538 1940.

to treat such patients with hormones instead of applying more sensitive tests for detecting diabetes. It seems as though the part which the various etiologic factors have been accused of playing depends on the various authors. Still, after the deduction of all the readily explainable cases of pruritus vulvae there remains a group which can be linked to hormonal disorders. It was suggested a long time ago^{1791 1795} mainly because of coincidence with menstruation, hypomenorrhea¹⁷⁹⁶ and particularly the menopause and castration^{1791 1797 1798}



Fig. 23. Kraurosis vulvae.

Lately, based on blood assays, unexpectedly high estrogen values in the menopause have been found together with pruritic conditions of the vulva.¹⁷⁹⁹ The frequent reports of successful treatment with estrogens have done much to establish the general opinion of a hormonal etiology.

It has been attempted to separate chronic pruritus vulvae, leukoplakia and kraurosis. Since transitional pictures are common and the same case may in its course pass through all the varieties, it is justifiable to deal with them

¹⁷⁹¹Jirocq L. Kraurosis. Bull. Soc. franc. derm. et syph. 1912, 41: 6. Ann. d. derm. et syph. Abstr. Dermat. Weh. schr. 62: 309, 1916.

¹⁷⁹²Tauig. Prenc. e rev. Lesions of the Skin of the Vulva. Leu. oplakie, Vulvitis, Kraurosis. Pruritu. Arch. Dermat. & Syph. 1: 671-635, 1910.

¹⁷⁹³Ferrari A. B. Presentazione di un caso clinico. Glor. Ital. derm. 68: 1466-1467, 1917.

¹⁷⁹⁴Laubhardt A. Pruritus Vulvae. Etiology and Therapy. Int. J. med. Wehnschr. 70: 121, 1914, 1916.

¹⁷⁹⁵Truhn E. Kraurosis Vulvae. Arch. f. Gynäk. 131: 574, 1914.

¹⁷⁹⁶Shut E. High negative Vol. ovag. Itis Associated With F. trog. n. Intl. Lanc. J. Obst. & Gynaec. Brit. Emp. 68: 447-494, 1912.

together. The disease starts with a subacute dermatitis of the vulva and often of the perianal area. There are exacerbations with oozing and widening of the involved area followed by regressions. Secondary infection especially folliculitis and irritation from scratching is common. A certain percentage of the cases may heal in this stage while others may develop a condition which is quite different from chronic eczema. The skin which was red and succulent before gradually acquires a leathery rigid character and cracks easily. It becomes more and more depigmented pearly or bluish white and dry. The hair the labia minora and the clitoris disappear. Finally atrophy of the vulva with white thin skin develops. The introitus vaginae may become contracted. Pruritus is present in all stages and on close inspection leukoplakia can be found in almost every instance.¹⁷⁹⁵ It is from these leukoplakic patches that cancer develops in more than fifty per cent of the cases. The histologic picture corresponds to the described clinical sequence. Hyperkeratosis acanthosis and inflammatory infiltration of the upper derma is followed by thinning of the epidermis and loss of pigment and elastic fibers. The papillae disappear completely. Many patients with chronic vulvar eczema never develop leukoplakia and kraurosis and cancer is rare in these nonleukoplakic cases.

Treatment of the pruritus vulvae based on the elimination of the mentioned etiologic factors is not often possible. Besides various local procedures estrogen therapy should be tried. The dosage advised has become higher and higher. Foss¹⁸⁰⁰ starts the treatment with injections of from 10 to 25 mg of estradiol benzoate twice weekly. As improvement occurs the injections are reduced to one a week. Smaller doses are necessary if local treatment in the form of ointment containing estrone estradiol or estradiol benzoate is used. Foss gives the following formula for the ointment.

Estradiol benzoate 10 milligrams in sesame oil mixed with 100 grams of a base consisting of

Halibut liver oil	20 parts
Cerae albae	16 parts
Adipis laeae	2 parts
Sodium borate	1 part
Ol amygdalae	41 parts
Aquae	20 parts

A great number of similar creams have been advised.^{1801 1802} The massaging into the thoroughly cleansed skin of 0.5 mg of estradiol in sesame oil seems a practical method.¹⁸⁰³ This should be done once daily by the physician. Later the patient may follow it up with an estrogen cream.

¹⁸⁰⁰Foss G L. Further Developments in Treatment (Pruritus Vulvae) *J Obst & Gynec Brit Emp* 46 771 45 1939

¹⁸⁰¹Klifton F. Treatment of Benign Pruritus and Kraurosis Vulvae by Simultaneous Local and Parenteral Administration of Estrogen. *J Clin Pharmacol* 3 218 '73 1943

¹⁸⁰²Lubowe I I. Stilbestrol (Estrogen) Cream in Pruritus Urol & Cutan. *Rev* 45 314-315 1941

¹⁸⁰³Schmitt-Nahsch V. Oestrogendiol (Estrogenic Preparation) in Therapy of Pruritus Vulvae. *Wien med Wchnsch* 85 904 909 1939

¹⁸⁰⁴Hertlikian A Y. Treatment of Chronic Pruritus With Local Applications of Estrogen. *New England J Med* 220 661-663 1939

Suppositories containing 0.36 mg. of dihydroxygestrin in 2 grams of cocoa butter have been found effective when inserted into the vagina once or twice daily.

It seems as if the initial enthusiasm about the hormone therapy of vulvar pruritus is subsiding.^{1800 1805 1806} It is certain that estrogen therapy not infrequently fails. The difficulty of finding out the suitable cases has led to the unsuccessful treatment of many cases. It is furthermore agreed that only few patients achieve complete and lasting comfort. Relapses which require further local therapy or a few injections are common. The more severe cases need almost continuous substitution therapy in one form or another.¹⁸⁰⁰ Some authors are reluctant to administer the estrogen locally over a long time because of the danger of producing cancer in a condition which is precancerous in itself. Finally adverse effects like uterine bleeding in menopausal women and local exacerbations are known to occur. However the fact remains that estrogenic therapy in many cases is one of the best methods we have for giving relief in a very annoying condition.

Similarly as in neurodermitis to which pruritus vulvae has other parallels the gastric hydrochloric acid has been found low or completely lacking in about one out of three cases. The more severe cases of kraurosis and leukoplakia are associated with achlorhydria.^{1800 1807} These cases seem to be benefited by regular HCl medication. Vitamin A in any convenient form¹⁸⁰⁰ and vitamin E or wheat germ oil in very high doses¹⁷⁹⁹ as well as vitamin B₁^{1801 1809} and uncooked diet have been recommended but not enough convincing experience has been forthcoming.

In discussing the internal therapy of the pruritic conditions of the vulva the importance of the various local methods such as antipruritic salves and lotions surgical procedures and radiation therapy should not be forgotten.

Miscellaneous—The great number of cases of eczema herpetiform eruption, pruritic attacks and other dermatoses which have been labeled as menopausal because they appeared in women at the age of forty to fifty five have rarely been investigated closely enough to corroborate this claim. Naegeli and Fellner¹⁷⁹¹ believe in a higher cutaneous sensitivity in the menopause just as is present during menstruation. This is supposed to account for many of the eczemas in middle aged women. High urinary prolactin does not prove more than the onset of the menopause and therefore does not confirm gonadal origin of the dermatosis in question. The best though still not a perfect proof is prompt cure after treatment with estrogen.¹⁸¹⁰

- ¹⁸⁰⁰ Naegeli N. Pruritus Vulvae, Leukoplakia and Kraurosis. J. Obst. & Gynaec. Brit. Emp. 69: 310-327, 1942.
¹⁸⁰¹ Fellner H. R. Pruritus, Leukoplakia and Kraurosis in Postmenopausal Women. Clin. North America 20: 109-116, 1940.
¹⁸⁰² Naegeli N. H. A. Hydrochloric Acid in Pruritus Vulvae. J. Obst. & Gynaec. Brit. Emp. 10: 1, 1976.
¹⁸⁰³ Kuncz D. Pruritus Vulvae. Vitamin A and Vitamin B₁—Complications in Therapy. Zbl. f. Gynäk. 66: 907-907, 1941.
¹⁸⁰⁴ Fymer H. Pruritus Vulvae. Deutsch. med. Wochenschr. 68: 961-96, 1942.
¹⁸⁰⁵ Leszczynski R. and L. J. Bhat. Dermatose bei Frauen auf hormonaler Grundlage. J. Dermat. 26: 132-4, 1931. Zbl. 41: 99, 1937.

A tendency to edema in various forms is an often mentioned climacteric manifestation. There are slight fugitive edemas of the extremities and also of the face which develop over night and disappear during day time.¹⁸¹⁵ Angioneurotic edema (Quincke's edema) is undoubtedly more common in the menopause and may then respond to hormonal therapy.

Urticaria factitia and an urticarial character of various types of dermatitis are often mentioned in connection with the menopause.



Fig. 1



Fig. 2

Fig. 1. 22. A. rated edema tinea testum (Haxthausen). Discrete palmar hyperkeratosis occurring also of edema frequently with obesity and hypertension following menopause (60 years old). Haxthausen (Copenhagen, Denmark).

Haxthausen¹⁸¹⁶ described as *keratoderma climactericum* ten cases of a dermatosis which he observed in women who besides the symptoms of menopause showed some degree of obesity, a normal basal metabolism, arterial hypertension and occasionally arthritis.

In the early stages the skin changes consist of lentil size, discrete, scaly keratoses apparently without inflammation. They are seen on symmetric spots of the palms and soles. Later they can hardly be differentiated from eczema.

¹⁸¹⁵ Curtschmann H. Über klimakterisches Oed. *in* Med. Klin. 38: 1, 6-7, 71, 1933.

¹⁸¹⁶ Haxthausen H. Keratoderma Climactericum. *Brit. J. Dermat.* 46: 181, 1934.

The relative frequency of *pemphigus* in the menopause has been emphasized¹⁸¹² The author is inclined to confirm this impression

Rosacea and telangiectases are often mentioned in connection with the menopause The same applies to Fox Fordyce disease to Poikiloderma atrophicum vasculare calcifications of the skin acrodermatitis atrophicans Raynaud's syndrome scleroderma erythema perstans trophedema^{1813 1816} xanthelasma and other dermatoses



Fig. 6. Dermatitis climacterica (Haxthausen) (from Fuchs F W Arch f Dermat & Syph 1943)

¹⁸¹² Werthel J Pemphigus Arch f Dermat u Syph 151 179 1926

¹⁸¹³ Milroy F W An Undescribed Variety of Hereditary Edema New York N J 88 505 1902

¹⁸¹⁴ Milroy F W Chronic Hereditary Edema J A M A 91 117 1918

¹⁸¹⁵ Chvostek F Xanthelasma und Ikterus Ztschr f klin Med 73 479 1911 Wl n klin Wchnschr 22 1630-163 1910

¹⁸¹⁶ Adlersberg D Beobachtung u bel in r au gedehuten Xanthomatose Arch f Dermat u Syph 148 500 19

CHAPTER XXVI

MISCELLANEOUS DERMATOSES WITH ENDOCRINE BACKGROUND

Dermatitis Dysmenorrhoea Symmetrica—In 1912 Matzenauer and Polland¹⁸¹⁷ published six cases of an unusual dermatitis in dysmenorrhoeic mostly young girls. The attacks or crops were not in connection with the menses. The lesions appeared in patches which were mostly round on the trunk and more oblong on the extremities. They were approximately symmetrical except in or close to the midline. The individual lesion started with a burning sensation followed by a pale red urticarial erythema the tinge of which was different from the early stage of ordinary dermatitis. Within half an hour the urticarial infiltration made the follicles stand out. Serum exuded into the follicles and formed a thin yellowish crust on the follicular orifice. These follicular lesions often coalesced within a few hours to form large weeping or crusty patches which were still slightly elevated because of their urticarial component and surrounded by a narrow inflammatory margin. Follicular extravasations often gave the patch a characteristic dotted appearance. The varying intensity of the changes could produce all degrees of inflammation running the gamut of exudative and hemorrhagic stages to the severe destruction of connective tissue with scar formation. The lesions healed quickly within a few days unless deeper destruction occurred which was rare. In these cases the picture and course was that of a dry necrosis and slow demarkation caused by an anemic infarct. The patches appeared most often on the face and less often on the hands arms legs and upper trunk. In one case the oral and laryngeal mucosa was involved.

Looking at the pictures of the original article one cannot help thinking of artifacts produced by striking or rubbing the skin with the fingers. The authors were fully aware of this impression and did everything imaginable to rule out self inflicted lesions¹⁸¹⁸. They observed some patches developing while the patient was asleep or under impervious dressings of zinc gelatin. The buccal and laryngeal lesions certainly could not be self inflicted. When a lesion was observed to appear on one leg the corresponding spot of the other leg was immediately covered by a zinc gelatine dressing. When this dressing was removed after two hours of constant medical watching a typical patch was found. It was impossible to produce typical lesions by mechanical and electrical irritation by spraying with ethyl chloride or by other methods.

All patients were suffering from *dysmenorrhoea*. The menses were irregular connected with many complaints and the flow scanty. Puberty and the onset

¹⁸¹⁷Matzenauer R. and Polland R. *Dermatitis Symmetrica Dysmenorrhoeica* Arch f Dermat u Syph 121 385 1912

¹⁸¹⁸Polland R. *Neue Beiträge zur Klinik der Dermatoses dysmenorrhoeica* Arch f Dermat u Syph 121 453-460 1912

small patch hidden under the hair to the size of a whole leg. The spots are often found on the nape of the neck, on the lower back and on the buttocks. They resemble the milk coffee spots seen in von Recklinghausen's neurofibromatosis. These areas of pigmentation indicate some relationship to the skeletal involvement. Unilateral bone disease is usually accompanied by ipsilateral pigmentations, widespread bone lesions by numerous and large pigmentations.



Fig. 23 — Albright's syndrome. Note areas of pigmentation. (Courtesy Wisconsin General Hospital.)

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CHAPTER XXVI

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¹⁸¹⁸Polland H. *Neue Beiträge zur Klinik der Dermatitis dysmenorrhoeica*. Arch f Dermat u Syph. 121 453-460 1921

of menstruation had often been late in one case precocious Psychopathic stigmata and functional circulatory disorders were noted

There is no doubt that the syndrome described by Matzenauer and Polland is an unusual one It must be very rare and the geographic distribution very uneven While the six original and two of the later cases of the conspicuous dermatosis were seen in the clinic in Graz Austria almost all the other cases so far about forty were seen in European and American centers which handle great numbers of patients Only part of the forty cases published so far closely resemble the original description^{181 183} The classical clinical picture of round oblong or fingershaped symmetrical patches does not seem to be a requirement anymore since cases of various types of dermatitis associated with ovarian disorders have been published as dermatitis dysmenorrheica This has apparently been done with the consent of Polland who in 1935 in an abstract written by him did not object to Urbach's^{1470 184} including some cases of erythroderma and neurodermatitis into the syndrome called Dermatitis dysmenorrheica

This depreciation of the morphology has come about by the progress achieved in determining the etiology of the menstrual dermatoses Urbach believes that the reactivity of the individual determines the morphology of menstrual dermatoses of a given dyshormonal causation Thus today the term dermatitis dysmenorrheica includes various dermatoses associated with menstrual disorders

Urbach and Kitamura¹⁸⁴ in their case of menstrual neurodermatitis labeled as dermatitis dysmenorrheica found the urinary excretion of gonadotropic substances increased while the estrogen content of the urine appeared to be lower than normal The patient was improved by estrogens and progesterone also by bleeding and laxatives The effect of the latter kind of treatment suggests a toxic factor According to Urbach it is occasionally possible to demonstrate that in dermatitis dysmenorrheica the premenstrual blood contains a substance which when injected into the skin of the patient during the intermenstruum will evoke an immediate urticarial reaction and a delayed response in the form of pinpoint sized papules clinically resembling the menstrual dermatosis Such a reaction could not be elicited in the patient with her own intermenstrual serum or with premenstrual serum from normal women Normal control persons did not respond to the premenstrual serum of the patient Probably as in the other menstrual dermatoses allergic as well as toxic and possibly neuro psychogenic factors may be of importance Pregnancy and cessation of the menses

Friedberg J Dermatitis symmetrica dysmenorrhoeica Urbach H Dermatol u Syph 111 173 1912

¹ Winkler F and Jakubowitz So-called Dermatitis Dysmenorrhoeica Arch Dermat u Syph 73 19 0

¹⁸¹ Witz E Gibt es ein pathologisch dysmenorrhoeische Hautkrankheit Arch f Dermat u Syph 136 36-47 1921

¹⁸² Hauck I Beitrag zur Dermatosi symmetrica dysmenorrhoeica (Matzenauer Polland) Wien m Wchnschr 75 316-319 9-10-19

¹⁸³ Lindner E Ueber die sog Dermatitis symmetrica dysmenorrhoeica Dtsch F Lang u 19 71 19 000

¹⁸⁴ Urbach P and Kitamura U Ueber pathologische Ausschüttung von Sexualhormonen bei einem Fall von Dermatitis dysmenorrhoeica (Polland Matzenauer) Klin Wchnschr 11: 271 274 1935

prevents the attacks. This has been demonstrated in several instances when after failure of other measures X ray castration was resorted to ^{1470 1923}

In several cases monthly attacks preceded the unusually late menarche and failed to appear later.¹⁸⁻¹⁸ In two cases of symmetric dermatitis dysmenorrheica marked prolanuria could be demonstrated.^{11,1}

The treatment should tend to correct any endocrine disorder. If this fails, the desensitization with premenstrual blood after the methods of Geber and Lehner and Rajka should be tried (see menstruation). Estrogen salve (5000 units per gram of Aquaphor) has been claimed to be successful locally.¹²⁹ Castration must be reserved for severe and intractable cases.

Fox-Fordyce Disease—The dermatosis in question is a chronic asymmetrical papular itching eruption involving the armpits and the pubic area. The axillary lesions form a diamond shaped palm sized group of closely set yet discrete firm shotty perioral papules of pinhead to pea size. The papules are of normal or pink color, only little excoriated and mostly arranged in beaded rows which cross the axilla. These grater like rows can be well demonstrated by stretching the skin. This dermatosis is with rare exceptions extremely itchy so that the axillary hair is usually rubbed off. Similar lesions occur though much less often in the pubic area and in the skin of the external genitalia and the navel. 1930

The pathologic changes consist of acanthosis, parakeratosis, keratosis and inflammation mainly surrounding the openings and lining the ducts of the apocrine sweat glands and of the hair follicles. The orifices of the involved glands are usually blocked by a keratotic plug.

The disease is quite rare and seems to affect pigmented races more often e.g. the Negroes and Jews (Jadassohn in discussion¹²¹). Only in a few (4) instances has it been observed in the male.^{122 123} The eruption is almost exclusively a disease of the menarche. It has never been seen before puberty at which period it sometimes starts.¹²⁴ The menopause may bring the trouble to an end¹²⁵ but the disease may also be provoked at this time.¹²⁶ The dis-

¹⁰ Berde I Fall von To i oderma m truale mit eryalp toidartigen Erach inungen Orr
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1^a Tragant J₄ Die symmetrische dym norholische \ krose Crón mód mevlana 21 11-1

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13 Rittschell, W. Zur B. handlung ovarieell bedingter Dermatos n mit Follikelatrophia
München med. Wchnscr. 1700 1937

101 Al sand A Fox Fordyce'sche Krankheit Handb d. H u Gk S 1 432-445 17
102 Pick W Zur Pathogenese d r Fox Fordyce hen Krankheit Arch f Dermat 17

165 IN 6 1932 Kaufman S N Fox Fordyce Dis as in M le New York State J Med Ex A

10 Kaufman R M Fox Fordyce-Prkrankung Zbl 38 454 1930
11 Steig R Lazal D Fo Fordyce-Prkrankung Zbl 38 454 1930
12 Tappin R G Fo Fordyce Dis ase Arch. f Dermat u Syph. 178 52-57 1936

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Fig. 2



Fig. 2a

Fig. 27-28. Fox-Fordyce disease. Courtesy Dr. Frank A. Van derbilt (Hill, New York).

order seems to improve in pregnancy.^{148, 157} Ovarian deficiency with amenorrhea, dysmenorrhea, infantilism, cystic ovary and other sexual dysfunctions have been described in the great majority of cases.^{1, 31, 152, 154} Premenstrual and menstrual exacerbations which may climax in violent pruritic spells is often mentioned. Hyperthyroidism¹⁵⁴ and hypothyroidism¹⁵⁴ have been found much less often than ovarian deficiency.



Fig. 3.—Fox Fordyce disease. Extremely itchy, but cleared up by x-ray treatment.

Considering the well known sexual relationship of the apocrine glands (see Puberty) and the evidence of accompanying ovarian disorders an ovarian etiology seems very probable. This is further supported by the response to estrogen therapy and in some cases prolation therapy.^{34, 6, 144, 154} Some authors believe that the condition is not curable and others think that roentgen therapy is the most effective treatment.

¹⁴⁷Gougerot and Bium: "Maladi de Fox Fordyce non pruriginose." *Bull. Soc. franc. de dermat. et syph.* 39: 700-701, 1932.

¹⁴⁸Loriat-Jakob and Gastinel: "La maladie de Fox Fordyce." *Bull. Soc. franc. de dermat. et syph.* 36: 17, 1932.

¹⁴⁹Kémerl: "Die Fox Fordyce'sche Krankheit." *Zbl. H.* 23: 11, 1931.

¹⁵⁰Johnson: "Fox Fordyce Disease." *Arch. Dermat. & Syph.* 12: 572, 1935.

¹⁵¹Goodman, M. B., and Solomon, M.: "Fox Fordyce Disease as Estrogenic Studies." *Arch. Dermat. & Syph.* 23: 907, 1939.

¹⁵²Gray, J.: "Hormonal Dysfunction in Fox Fordyce Disease." *Gynec. hemat.* 52: 50-59, 1939.

¹⁵³Abel: "Dermat. Ztschr." 77: 124, 1934.

¹⁵⁴Prumark: "La maladie de Fox Fordyce." *Ann. f. dermat. et syph.* 6: 949, 1931.

¹⁵⁵Reinold, F.: "Corpus Luteum Hormone Therapy (Furunculosis)." *München. med. Wch. schr.* 87: 42-43, 1940.

¹⁵⁶Roburgh, A. C.: "A Case of Fox Fordyce Disease." *Brit. J. Dermat.* 55: 121, 1943.

¹⁵⁷Kerlitz, C.: "Hormones in Therapy of Fox Fordyce Disease." *Dermat. Wchnschr.* 113: 733-736, 1941.

Albright's Syndrome—This typical combination was first recognized by Fuller Albright¹⁹⁴⁷ who described a triad of disseminated osteitis fibrosa areas of cutaneous pigmentation which have a distribution suggesting some connec



FIG. 30. Albright's syndrome. Areas of pigmentation and precocious puberty. (From Albright & Butler. *A M. Hampton A O and Smith P. N. W. England J Med.*)

tion between them and the bone lesions and sexual and somatic precocity when the disease occurs in the female sex. Pathological fractures are common

¹Albright F, Butler A M, Hampton A O and Smith P. Osteitis Fibrosa Disseminata, Areas of Pigmentation and Endocrine Dysfunction With Precocious Puberty in 3 males. *N. Y. J. Med.* 216: 1-40, 1957.

According to Iichtenstein and Jaffe ¹⁹⁴⁸ who reviewed ninety cases among them fifteen of their own the syndrome is not extremely rare if one includes the incomplete cases. The disease affects girls more often than boys the ratio being about 3:2. The first symptom is often a pathological fracture which leads to x ray examination of the bones. Scattered but often unilateral patchy cystlike lesions of osteitis fibrosa are found. There are always parts of the skeleton showing normal bones ^{1949 1950}



Fig. 31. Alt light 3 d om 6 t ill 6 t rosa dier minat 11 om Alt light 3 New England J Med

In the female sexual precocity with early onset of menstruation and development of secondary sex characteristics and early bone age occurs in about one third of the cases.¹ The sexual development in the male patients is normal. In the skin there are smooth brown nevus like patches of oblong round or jagged type. They vary in size from a group of freckle like spots or a single

[illegible]

small patch hidden under the hair to the size of a whole leg. The spots are often found on the nape of the neck, on the lower back and on the buttocks. They resemble the milk coffee spots seen in von Recklinghausen's neurofibromatosis. These areas of pigmentation indicate some relationship to the skeletal involvement. Unilateral bone disease is usually accompanied by ipsilateral pigmentations. Widespread bone lesions by numerous and large pigmentations.



Fig. 23. Albright syndrome from view to a case of pigmentation. (Courtesy Wilcox Memorial Hospital.)

The blood calcium and blood phosphorus are normal; this is important in the differentiation of hyperparathyroidism. In spite of at least twenty-five recorded explorative operations, a parathyroid tumor has never been found. The differential diagnosis has to rule out neurofibromatosis, Hand-Schüller-Christian's xanthomatosis, Paget's disease, multiple hemangiomas of the bones and some other rare conditions. The diagnosis is easy if the classic triad of bone disease, pig-

mentation and precocity in the female is present. Several patients started life with icterus gravis neonatorum which persisted for months.^{183 185}

The etiology is unknown. An embryonic defect (Albright) seems likely. The twin brother of one patient was normal. In some cases a positive Babinski suggests a participation of the nervous system.¹⁸³

The prognosis of the disease should be guarded but not too pessimistic. In one case precocious puberty was followed by normal adult sex life with the consequent production of a healthy child. The bone disease may become arrested. The individual bone lesion is amenable to surgical treatment.

It is of interest that Lena Medina of Peru who gave birth to a child at the age of five probably represented such a case of Albright's syndrome. Her attending physician Dr Gerardo Lozada of Pisco Peru informed Dr Albright that she had both the brown spots and bone changes together with the precocity.

Geroderma Genito-Dystrophicum. Progeria.—In this rare syndrome which has been seen starting early in life in both sexes the most striking feature is the senile appearance of the skin and particularly of the face. There are many fine wrinkles, the skin is flaccid yellowish and the subcutaneous fat and the muscles on the distal parts of the extremities are usually extremely reduced. The hair is either completely lacking or restricted to the scalp. The skin gives a senile atrophic impression which make children or relatively young persons look old. Diffuse and early arteriosclerosis is a characteristic feature. Generalized pigmentation has been seen. The nails are thin and brittle. The skeleton is either eunuchoid or dwarfed. The intelligence is intact. Many endocrine symptoms like diabetes insipidus exophthalmos polyphagia and amenorrhea have been described. The testicles are atrophic. Aplasia or atrophy of the thyroid and tumor or sclerosis of the pituitary have been found at autopsy. The disorder is probably related to Simmonds's disease in which precocious senility is also a feature.¹⁸⁴ In spite of the severe changes the mentality remains alert and the patients may live for many years.^{185 186} A syndrome of infantilism with web formation of the skin along the neck is known as *Turner's¹⁸⁷ syndrome*. In one autopsy case¹⁸⁸ no functioning ovarian tissue could be found. There was no axillary hair present and the pubic hair was scanty.

Scleroderma Poikiloderma, Acrodermatitis Atrophicans.—The voluminous literature on these rare dermatoses is replete of reports on accompany

¹⁸¹ Hall I. Osseous Dystrophy Following Icterus Gravis Neonatorum. Arch Dis Childhood 151 107 1939

¹⁸² Sommerfeldt P and Brown A. Osteodystrophia fibrosa. Am J Dis Child 57 90 101 1939

¹⁸³ Docke M B M yerdling H W and Wallace O T. Albright's Syndrome. Proc Staff Meet Mayo Clinic 81 83 1944

¹⁸⁴ Curschmann H. Die Simmondsche Krankheit. Med Klin. 22 895-897 1936

¹⁸⁵ Marinenco G and Parhon C I. Su un cas de diabete insipido avec cachexie hypophysaire infantilisme senilisme atrophie des organes genitaux et convulsions de type epileptique. Rev franc d'endocrinol 11 105 146 193

¹⁸⁶ Thannhauser J. Werners Syndrome (Progeria of the Adult) and Rothmund's Syndrome. Ann Int Med 11 539-606 1943

¹⁸⁷ Turner R H H. A Syndrome of Infantilism. Congenital Webbed Neck and Cubitus Valgus. Endocrinology 23 68-74 1939

¹⁸⁸ Sharpey-Schafer H P. Pterygonuchal Infantilism (Turner's Syndrome). With Postmortem Findings. Lancet 2 559-560 1941

ing and often contradictory endocrine symptoms although no definite relationship has evolved. In *scleroderma* the most frequently observed and best founded systemic relationship is a disturbance of the *calcium* metabolism. Thibierge and Weissenbach¹⁸⁵⁵ demonstrated calcium deposits in the sclerodermatic skin. Later this observation was often confirmed^{1860 1861} but its significance denied again more recently.¹⁸⁶ The blood calcium and also the phosphorus were often found to be above normal^{1863 1868} and the tolerance to calcium, expressed by the ability to restore the normal calcium level in the blood after injection of calcium was found disturbed.¹⁸⁶⁷ Both calcium and phosphorus are retained in the body in *scleroderma*¹⁸⁶⁶ which is not in line with the negative calcium balance in hyperparathyroidism to which the relation seemed suggestive.¹⁸⁶⁶ The Hamilton Schwartz test for parathyroid hormone showed high values in the circulating blood in two out of three cases of so called *Werner's syndrome* (adult progeria). This syndrome is a rare heredo-familial disease in which *scleroderma*, blue sclerae, hypogonadism, trophic ulcers, metastatic calcification, osteofibrosis and other endocrine stigmata are the main features.^{1864 1869} The Hamilton Schwartz test was negative in two ordinary cases of *scleroderma*.¹⁸⁷⁰ There is some evidence in support of hypoparathyroidism in *scleroderma*¹⁸⁷¹ in the rare cases of its association with tetany.

Primary atrophic and absorptive changes^{187 1873} prior to the *scleroderma* in the *phalanges* and in the distal ends of other bones¹⁸⁷⁴ *osteomalacia*^{1875 18 6}

¹ Thibierge and Weissenbach. Concrétions calcaires sous-cutanées et sclérodémie. Ann de dermat et syph 11 9 1911

¹⁸⁶⁰ J. ennéty R. L. J. Calcino is and Scleroderma. Treatment by ketogenic Diet J. Pediat 1 607-673 1933

¹⁸⁶¹ Pautrier L. M. Sclérodémies chloïdes et calcémie. I. Revue méd 41 345-347 1933

¹⁸⁶² Kaether H. and Kaether H. W. Ca Gehalt normaler Haut v. rgl. h. n. mit den Befunden bei Scleroderma. Klin. Wchnsch. 19 353-3 4 1940

¹⁸⁶³ Jung A. and Hakki A. C. Études sur la calcémie. Rev. de chir 61 53 48 193

¹⁸⁶⁴ Hillmann H. Beitrag zur Kenntnis der Sclerodermie. Diss. Hamburg 1930

¹⁸⁶⁵ Leriche H. Jung A. and D. Bailey M. The Surgical Treatment of Scleroderma. Sym. pathectomy and Parathyroidectomy. 26 Cases. Surgey 1 6 1937

¹⁸⁶⁶ Cornbleet T. and Glick H. C. Calcium Metabolism in Scleroderma. Arch. Dermat. & Syph 25 184 1937

¹⁸⁶⁷ Rothman S. and Weiss I. Calciumbalance problem bei Sclerodermie. Klin. Wchnsch. 19 1 45-156 1931

¹⁸⁶⁸ Burch G. E. Scleroderma. Symposium. New Orleans M. & S. J. 92 1 21 1933

¹⁸⁶⁹ Oppenheim B. S. and Ingel V. H. Werner Syndrome. Am. J. M. Sc. 202 6 9-642 1911

¹⁸⁷ Winer N. H. The Hamilton Schwartz Test and Hypoparathyroidism in Scleroderma. Am. J. M. S. 202 61-650 1933

¹⁸⁷¹ Marmon H. Sclerodermie et parathyroïdes. Gaz. d. hôp 185 375 19 9

¹⁸⁷² Harkony T. and Eisch F. Beiträge zur Kenntnis der Akroostose. Fortsch. a. B. C. b. d. Röntg. strahl. n. 47 247 293 1933

¹⁸⁷³ Leitch R. and Jung A. Nature et origine de la sclérodémie. Bull. Soc. franc. de dermat. et syph. 42 4 3-49 1935

¹⁸⁷⁴ Leitch J. M. and Falgout and Georges. Le cas de sclérodémie avec gros troubles de localisation. Rcl. des parathyroïdes. Bull. et mém. Soc. méd. d. Hôp. de Paris 53 921 9 9 1937

¹⁸⁷⁵ Morawicka J. In and maladie de Basedow associée à l'hypercalcémie et à l'ostéomalacie. Rev. neurol. 1 217 2 19 4

¹⁸⁷⁶ Stilling W. Die hypotrophische und der osteomalische Typus der Scleroderma-tischen Drogenration. Int. ka. 1 k 7 99-103 19 4 Zbl. 27 151

bilateral cataract^{1856 1877 1879} the experimental production of scleroderma like skin changes in young rats and pigs following injection of parathormone^{1880 1881} and finally the relatively successful *treatment of scleroderma* by unilateral *parathyroidectomy*^{188 188 1884} have given support to a *hyperparathyroid* etiology, especially since some of the excised parathyroids were found hypertrophied or inflamed¹⁸⁸⁵ However the results of parathyroidectomy are still controversial¹⁸⁶⁸

There are many observations suggesting *other endocrine dysfunctions* Amenorrhea dysmenorrhea^{1889 1896 1897} onset of the disease in pregnancy and in the spontaneous and induced menopause^{1 38 1889 189} findings of ovarian changes the therapeutic success of estrogens,^{1893 1896} and the 3 1 predominance of the female sex¹⁸⁹⁶ are reasons enough to consider the *gonads*. The situation is similar with regard to the pancreas thyroid¹⁸⁹⁷ and pituitary. It is now generally accepted that *acrosclerosis*¹⁸⁹⁸ or *sclerodactylia* is essentially different from the diffuse or localized scleroderma (morphes). According to Seller¹⁸⁹⁰ *acrosclerosis is a vegetative neurosis* and is related to Raynaud's disease. True *scleroderma* however seems more likely to be a *fermentative disorder* related to the *pancreas*. It has in some instances been successfully treated with pancreas liver stomach and duodenum extracts (Seller¹⁸⁹⁰ and many other articles by the same author)

¹⁸⁷⁷ Jébe E Hartmann E and Thibaut F. Le cas familial de syndrome de sclérose mixte avec cataracte troubles endocriniens et neuro-végétatifs au crâne. Rev. neurol. 1 606-618 1930. Zbl 36 21

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¹⁸⁹⁷ H. R. H. M. R. H. J. Oat. Hie J. H. Parathyroidectomy for Raynaud's Disease and Scleroderma. Ann. Surg. 101 1012 1935

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¹⁸⁹⁹ Grzybow H. Scleroderma diffusa. Sclerodactylia und Scleromyositis. Zbl 38 461 1930

¹⁸⁹⁰ Hau Prussakowa G. Degenerationis genito-sclerodermae. Warsz. Czas. lek. 2 1 19 1931. Zbl 38 56 10 8

¹⁸⁹¹ Plitz R. Scleroderme und Psoriasis bei Cravkittät und Menstru. Klin. Zbl 17 20 1925

¹⁸⁹² Vallée A. Scleroderme et plaques de la peau. (Essai physiopathologique). Strasbourg méd. (pt. 2) 85 207-224 10 7 1926 59

¹⁸⁹³ Hoenb. f. Scleroderma. Zbl 38 619

¹⁸⁹⁴ L. J. K. Scleroderme. Zbl 38 657

¹⁸⁹⁵ Harri. R. P. and Lichtwitz A. Scleroderme. Zbl 38 2 193

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¹⁸⁹⁷ Szary A. and Horowitz. Treatment of Scleroderma With Ovarian Hormone and Autohemotherapy. Bull. Soc. française de dermat. et syph. 41 69-71 1934. Abst. H. nat. Ztschr. 70 181 1934

¹⁸⁹⁸ Phrmann G. and H. R. H. Scleroderme. Handb. d. H. n. Ck. 8 2 717 9 3 1931

¹⁸⁹⁹ Rothman S. F. dokrine. Scleroderma bei Scleroderme. Klin. Wchnsch. 4 1691 1930

¹⁹⁰⁰ Sell J. Sclerodactylie progressiv. Scleroderme (Akrochlo rose). Dermat. Ztschr. 61 139 146 193

ing, and often contradictory endocrine symptoms, although no definite relationship has evolved. In *scleroderma* the most frequently observed and best founded systematic relationship is a disturbance of the calcium metabolism. Thibierge and Weissenbach¹⁵⁴ demonstrated calcium deposits in the sclerodermatic skin. Later this observation was often confirmed^{155,156} but its significance denied again more recently.¹⁵⁷ The blood calcium and also the phosphorus were often found to be above normal^{158,159} and the tolerance to calcium expressed by the ability to restore the normal calcium level in the blood after injection of calcium was found disturbed.¹⁶⁰ Both calcium and phosphorus are retained in the body in *scleroderma*¹⁶⁰ which is not in line with the negative calcium balance in hyperparathyroidism to which the relation seemed suggestive.¹⁶¹ The Hamilton-Schwartz test for parathyroid hormone showed high values in the circulating blood in two out of three cases of so-called *Heerdt's syndrome* (adult progeria). This syndrome is a rare hereditary condition in which *scleroderma*, blue sclera, hypoparathyroidism, trophic ulcers, metastatic calcification, osteodystrophia and other endocrine symptoms are the main features.^{162,163} The Hamilton-Schwartz test is negative in two ordinary cases of *scleroderma*.¹⁶⁴ There is some evidence in support of hypoparathyroidism in *scleroderma*¹⁶⁵ in the rare cases of its association with tetany.

Changes in the phosphate and absorptive changes^{166,167} proper to the *scleroderma* in the phalanges and in the distal ends of other bones¹⁶⁸ are common^{169,170,171}

¹⁵⁴Thibierge, J. and Weissenbach, J. "Les dépôts calciques sous-cutanés et sclérodermie." *Ann. de l'Inst. et. 307* p. 179, 1931.

¹⁵⁵Klein, R. and J. B. J. "Calcium in *scleroderma*. Treatment by high-grade Diet." *J. Pediat.* 11: 66-68, 1937.

¹⁵⁶Fautour, L. M. "Le traitement des lésions sclérodermiques." *Pres. méd.* 41: 245-51, 1933.

¹⁵⁷Kauffmann, H. and H. K. W. "Calciumhalt des Blutes bei der Sklerodermie." *Arch. Dermat. u. Syph.* 29: 253-5, 1940.

¹⁵⁸Jung, A. and H. K. W. "Fälle von Hyperkalzämie." *Arch. Dermat. u. Syph.* 81: 13-14, 1935.

¹⁵⁹Hillman, H. "Beitrag zur Kenntnis der Sklerodermie." *Dtsch. Dermat. u. Syph.* 1930.

¹⁶⁰Leitch, R. Jung, A. and J. D. L. "Surgical Treatment of *scleroderma*." *Symposium on the Pathology of the Skin*, 1937.

¹⁶¹Leitch, R. and J. D. L. "Calcium Metabolism in *scleroderma*." *Arch. Dermat. u. Syph.* 25: 184-193.

¹⁶²Hillman, H. and W. K. W. "Calcium metabolism in *scleroderma*." *Klin. W. chn.* 10: 1-11, 1931.

¹⁶³Hillman, H. and W. K. W. "Calcium metabolism in *scleroderma*." *Klin. W. chn.* 10: 1-11, 1931.

¹⁶⁴Leitch, R. and J. D. L. "Calcium metabolism in *scleroderma*." *Klin. W. chn.* 10: 1-11, 1931.

¹⁶⁵Leitch, R. and J. D. L. "Calcium metabolism in *scleroderma*." *Klin. W. chn.* 10: 1-11, 1931.

¹⁶⁶Leitch, R. and J. D. L. "Calcium metabolism in *scleroderma*." *Klin. W. chn.* 10: 1-11, 1931.

¹⁶⁷Leitch, R. and J. D. L. "Calcium metabolism in *scleroderma*." *Klin. W. chn.* 10: 1-11, 1931.

¹⁶⁸Leitch, R. and J. D. L. "Calcium metabolism in *scleroderma*." *Klin. W. chn.* 10: 1-11, 1931.

¹⁶⁹Leitch, R. and J. D. L. "Calcium metabolism in *scleroderma*." *Klin. W. chn.* 10: 1-11, 1931.

¹⁷⁰Leitch, R. and J. D. L. "Calcium metabolism in *scleroderma*." *Klin. W. chn.* 10: 1-11, 1931.

¹⁷¹Leitch, R. and J. D. L. "Calcium metabolism in *scleroderma*." *Klin. W. chn.* 10: 1-11, 1931.

Among the many endocrine symptoms which have been reported in connection with the rare *poikiloderma atrophicans vasculare* the relatively frequent onset in the *menopause* seems worthy of mention.¹⁷¹ The same is true of *acrodermatitis atrophicans*. In this dermatosis which is not very rare in some parts of Europe, the females outnumber the males 2:1.¹⁷² There are some observations of *acrodermatitis atrophicans* in Graves' disease.¹⁷³

Acrocyanosis — *Erythema venosum*¹⁷⁴ *Erythrocyanosis symmetrica*¹⁷⁵
Erythrocyanose symétrique malléolaire des jeunes filles

Symmetrical sometimes circular palm sized cyanotic plaques almost exclusively occurring in young girls¹⁷⁶ have been described under several names.¹⁷⁷ The plaques are mostly seen anteriorly or laterally on the lower legs less often on the inner aspects of the thighs right above the knees. The lesions are bluish red sometimes with bright red (cinnabar) spots¹⁷⁸ and some thin telangiectases. The erythema vanishes on pressure. The skin is taut and cannot be folded. The lanugo has usually disappeared. There is an ill defined deep firmness which gives a doughy impression though there is no pitting. The lesions are cooler to the touch than the normal skin. Superficial ulceration has been seen but this is rare.¹⁷⁹ Local fat increase has been described.¹⁸⁰ There is only minimal nonspecific inflammation around the vessels. Capillaroscopy reveals varicosities of the capillary veins and frequent spasms.¹⁸¹ The course is an extremely chronic one. The lesions appear in the winter time improve in summer to some extent and reappear with the first frost. Like many lower leg conditions they are better after a night's rest and worse again in the evening. The dermatosis is clinically closely related to chilblains from which it differs in the site and the accompanying circumstances which make an ovarian relation probable.¹⁸² The patients are overwhelmingly young girls and women up to about thirty years of age.

Children do not seem to become affected though they are very susceptible to chilblains. Irregularities of menstruation¹⁸³ obesity¹⁸⁴ and other endocrine

¹⁷¹ Jessner N and Löwenstamm A. Bericht über 66 Fälle von Akrodermatitis chronica atrophicans. *Deut. Monat. Wehnschr.* 77: 1169, 1934.

¹⁷² Bezecey H and Berlin F. Étologie de l'Acrodermatitis atrophicans. *Hersheimer Klin. Wehnschr.* 12: 276-277, 1933.

¹⁷³ Friedman W I. Scleroderma. *Arch. De mat. & Syph.* 19: 901-916, 1939.

¹⁷⁴ Ochen A and DeBakey M. Peripheral Vascular Disease. *Treatment Surg. Gynec. & Obst.* 70: 1055-1072, 1940.

¹⁷⁵ Ochen A and DeBakey M. Scleroderma. *New Orleans M. & S. J.* 82: III 24, 1939.

¹⁷⁶ Leffell H. Erythema venosum. *München Med. Wehnschr.* 67: 967, 1930.

¹⁷⁷ Holt F. Erythrocyanosis cutis symmetrica. *Klin. Wehnschr.* 1: 578-580, 1937.

¹⁷⁸ Lillmo A. Erythro-cyanose symétrique des malléolaires des jeunes filles. *Thèse de Strasbourg* 1939.

¹⁷⁹ Nicolas J and Petouraud Ch. Erythro-cyanose symétrique des malléolaires des jeunes filles. *Nouvel. pratique dermatologique* Vol 5 Paris 1936. Masson & Cie pp 339-395.

¹⁸⁰ Lortat-Jacob Solente G and le Baron. Erythro-cyanose des membres inférieurs. Présence de taches claires. Leur provocation réflexe. *Bull. Soc. franç. de dermat. et syph.* 28: 190-191, 1931.

¹⁸¹ Baer T. Stauungsdermatosen. *Zbl.* 43: 603.

¹⁸² Ward III L. Contributo alla conoscenza del fenomeno di eritrocianosi degli arti inferiori. *Glor. Ital. di dermat. e sif.* 69: 81, 1935.

¹⁸³ Künig. Akrocyanosis cruris. *Zbl.* 32: 416, 1930.

¹⁸⁴ Seifert and Lichten F. Erythrocyanosis extremitatis chronica. *Arch. f. Dermat. u. Syph.* 126: 27, 1928.

stigmatalike hyperhidrosis of palms and soles. Marfan's¹²¹ main hypoglandular dry skin, gutter¹²² and adrenal hypotension¹²³ have often been observed.^{124, 125, 126} The condition has also been seen after castration¹²⁷. Estrogen therapy and thyroid have been helpful in many cases. Yet no entirely convincing endocrine relationship has so far been established. Tuberculosis¹²⁸ has been considered since some cases developed into tuberculosis indurata¹²⁹. The condition seems to be rarer in the United States than in the corresponding climates in Europe.

¹²¹Marfan G. The Hyperostotic Hand (Chirurgie et Pédiatrie) 66 p. 45 1921 Zbl 2 209

¹²²Thomas J. L'acrocyanose dans la période urinaire néphrétique de la lésion f. Néphr 21 123 193 1921 Zbl 2 413

¹²³Chapoy J. L'acrocyanose ne permet pas de faire que l'acrosyndrôme f. Néphr 21 165 19 4 Zbl 2 381 1921

¹²⁴Galant J. M. Fall v. Hyperostosis m. Viret Arch f. path. Anat 267: 614-633 19

¹²⁵Alpert M. and Gilman P. M. L'acrocyanose des membres inférieurs. Importance phylo-pathologique et pathogénique de l'hypertrophie v. l'urémie et l'hypertrophie des reins Arch. d. Méd. 1 293 23 1922 Zbl 2 313 320

¹²⁶Green M. Mier tro II Dermat. mon. Dermat. Ztschr 11 700 193

¹²⁷Juicer P. Les dystrophies f. f. et v. la lésion dystrophique notique des neuro-muscles et les. Bull. Soc. franç. d. dermat. et yph 22: 34-35 1924

¹²⁸Asanaka H. et Nakachi O. L'empyème du trochantère dans l'acrocyanose. Chir. Ital. II Dermat. 22 4 413 1922

CHAPTER XXVII

AGEING*

Senile atrophy of the skin starts shortly after the age of forty¹⁹¹⁵. The epidermis becomes thinner at the expense of the lower strata. The horny layer appears looser. The mitoses in the basal layer become scarcer or disappear completely and the cells of the basal and prickle cell layers show perinuclear vacuolization. The stratum granulosum is hardly discernible.¹⁹¹⁷ The papillae flatten and lose their elastic fibers. The collagenous fibers grow thinner and stain poorly. The elastic fibers show clumping shortening thickening and irregular positions together with marked hyperplasia especially in the face and neck. This hyperplasia of the elastic tissue may account for the yellowish tinge of the face and hands in some old people.¹⁹²⁶

Elastin collastin and collatin are often present.¹⁹²⁷ The peculiar accumulations of elastic fibers in the facial skin known as elastica mimica¹⁴²⁰ which develop at puberty and reach their highest development at thirty are definitely regressive at forty. At sixty the alterations of the elastica are marked.¹⁹²⁸ The elastic fibers of the blood vessels especially of the elastica interna participate in the changes. The senile changes in the elastic fibers seem to depend on exposure to light and elements since they were not found in unexposed skin of old people.¹⁹²⁹

Extravasation on slight trauma (*purpura senilis*) is common.

Severe arteriosclerotic changes may be observed along with corresponding senile changes in other organs.

The *sebaceous glands* are reduced in number and they show certain qualitative changes. In the face especially on the nose and forehead hyperplasia of the sebaceous glands is common after the age of forty. The hair follicles are often found without hair and the muscoli arrectores pilorum are usually atrophic. The subcutaneous fat shows degeneration.¹⁹²⁷ The water content of the senile skin is reduced.^{1932 1940} and the rate of insensible perspiration is lower than in young subjects.¹⁹⁴¹ The capillary reactivity to mechanical and other stimuli

*See also at the end of the book.

¹⁹¹⁵ Evans R, Cowdry E V and Wilson P E. Ageing of Human Skin. Influence of Dermal Shrinkage on Appearance. *J. Epid. and Infection* in Young and Old. *Fixed Tissues Anat. Rec.* 55: 545-565, 1943.

¹⁹¹⁷ Cowdry E V, editor. *Problems of Ageing*, ed. 2, Baltimore, 1941. Williams and Wilkins Co. Chapter on skin by J. D. Weidman.

¹⁹²⁶ Haus M M. Changes in the elastic skin. *Ukrain. med. Arch.* 8: 1. III: 105, 1932. Zbl. 45: 659.

¹⁹²⁷ Jirli I. Differences in the Elastic Fibers of the Skin According to Race and Age. *Jap. J. Dermat. & Urol.* 40: 716-721, 1935. *Abstr. Arch. Dermat.* 37: 661, 1938.

¹⁹²⁸ Hill W R and Montgomery H. Regional Changes and Changes Caused by Age in Normal Skin. *J. Invest. Dermat.* 3: 231-245, 1940.

¹⁹²⁹ Bürger M and Schlomka G. Chemische Gewebeforschung für die Altersforschung. *Klin. Wchnschr.* 7: 1944-1945, 1945.

¹⁹⁴¹ Burch C E, Cohn A E and Neumann E. Rate of Water Loss From Fingertips and Toes. *Tip in Normal Seniles etc.* *Am. Heart J.* 22: 185-196, 1942.

is slow in response and slow in return to the normal status.^{190 191} Cavallucci who systematically studied the *physiological reactions* of the senile skin in comparison with that of the middle aged found red dermographism delayed and urticaria factitia less frequent and less pronounced. Marston's sign (see thyroid) the pilomotor reaction and the urticarial intracutaneous morphine reaction are also less marked. Senile atrophy causes decrease of the sensitivity to touch pain and temperature. The fact that old people suffer from cold more than young person is not due to increased sensitivity but to other probably vascular factors.



Fig. 73. *Parvula senilis*

The cutaneous manifestations of ageing are of practical importance for the *objective determination* of the age.^{192 193} At the age of 20 the facial skin is still free of wrinkles. The cheeks are rounded so that the mouth and nose appear small. At 25 the forehead and the lower lids show the first wrinkles and the nasolabial folds become apparent. The veins of the back of the hand begin to show.¹⁹⁴ At 30 crow's feet appear at the lateral angles of the eyes. The beard growth is most vigorous between 30 and 40. At this age men often become more hairy on the chest, arms and the dorsa of the hands. The occipital hairline loses its sharpness.

The thirty-fifth year usually marks the first folds in front of the ears. (Nude-shdin after Sebestian)¹⁹⁵ The preauricular wrinkles increase in length more than in depth so that some criminologists have attributed much importance just to the length of these folds.¹⁹⁶ Graying of the hair at the temples and a less

¹⁹⁰ Jettmann R. *Altveränderungen am Gefäßendabschnitt der Lippenachleimbaut* *Ztschr f Anat u Entwicklungsgeoch* 93 660-677 1930 Zbl 37: 600

¹⁹¹ Cavallucci U. *Anatomia e fisiopatologia della cute* *Reattività della cute senile* *Glor Ital Med dermat e sif* 75 575-579 1934

¹⁹² Sebestian V. *Ueber objektive Altersschätzung am lebenden Erwachsenen* *Dis Bonn* 1927

¹⁹³ Müller L. B. *Altersschätzung des Menschen* Berlin 1923 Julius Springer

rosy and more ruddy hue of the cheeks may become noticeable in the fourth decade. The age of graying varies widely. A familial factor can often be recognized.

A person of 40 already has most of the typical wrinkles. The preauricular wrinkles are now multiple and extend upward to the upper level of the tragus. The cervical folds which run from the chin down to the jugulum may be seen in lateral light.

At 45 the suborbital wrinkles become more marked. In light coming from the side the cervical folds can now be clearly seen. The lips start to become thinner. In a fat person the double chin is marked and in a lean person the cervical skin becomes too wide.¹⁹⁴ The eyebrows may become bushy or at least a few long hairs may grow.



Fig 234



Fig 235

Fig 234—Female aged 65 years. Long ear preauricular wrinkles.

Fig 235—Cervical and other folds and wrinkles.

In the early fifties all the wrinkles grow deeper. The hands become wrinkled. Small wrinkles of the bridge of the nose, of the ear lobe and of the chin are present. The entire skin is now relatively dry. The graying of the hair can no longer be concealed by pulling out of the white hairs.

Senile hyperpigmentation starts around 55. Wrinkles on the bridge of the nose, the ear lobes and the chin become marked. The longitudinal cervical folds are accented. The rhomboidal crossing folds in the nape of the neck (*Cutis rhomboidalis*) are seen in some men, especially those who live an outdoor life.

In the sixth decade the teeth appear to be longer because of atrophy of the alveolar ridge.

At 60 the first radial wrinkles around the mouth appear on the upper lip. The cheeks become loose and droopy. The glans penis becomes smaller and the penile skin wrinkled and darker. The pubic hair in the male appears thin and less curly, though possibly spread over a wider area than in younger years. The scrotum is longer and more flaccid and fails to contract on exposure to cold, probably because of atrophy of the tunica dartos.



Fig. 36

Fig. 37

Fig. 36. Male aged 87 years. 1. Hair on the eyebrows ill pronounced. 2. Pigmented spot.

Fig. 37. A small fold of lips is ill appeared. Wrinkles round lips.

In the female analogous regression of the third major takes place. The subcutaneous fat is often accumulated around the hip, leaving the extremities and the chest relatively lean. The formation of the arcus senilis corneus begins.

Around 65 the hair growth in the ear ducts, the nostril, and on the nape of the neck becomes more conspicuous in men as well as in women. The bristly hypertrichia on the chin is often marked in the female sex.

At the age of 70 the facial wrinkles are often found crossing each other. Sometimes they form a netlike pattern or a papyraceous wrinkling like that seen in castrates. Senile pigmentations have increased. The skin is thin and a fold lifted from the back of the hand returns but slowly to the normal position. The head hair is usually thin or has disappeared. Complete senile baldness is occasionally seen in women also.



Fig 238 — Female aged 80 years. All wrinkles are developed. Drooping upper lid. Veins visible in the lips have disappeared.



Fig 239 — Male aged 76 years. Senile atrophy of the skin.



Fig. 210 — Male aged 80 years. Multiple keratoma, basal cell epithelioma of nasolabial fold. Crow's feet lines around the mouth. Vermilion border has disappeared.



Fig. 211 — Male aged 86 years. The long ear of old age.

The thinning of the lips is completed at 75 so that hardly any vermilion can be seen. The thin mouth appears longer and sunken because of the atrophy of the alveolar ridges and the loss of the teeth. The backs of the hands are wrinkled like thin paper.



Fig. 24 — Mouth aged 75 years. Tongue thin of old age.

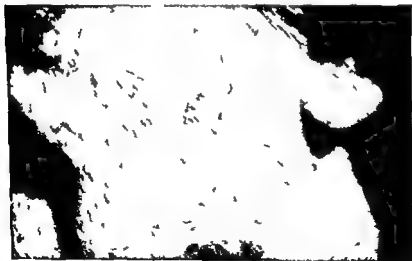


Fig. 43 — Senile pigmented spot.

The eighties are characterized by the tired expression of the eyes caused by the drooping upper lid (senile ptosis). The radial wrinkles around the mouth are conspicuous. The cervical folds which appeared long before are very marked. The ears not only appear longer but are actually larger and flabby. The nose



Fig. 42 — cell carcinoma



Fig. 43 — cell hemangioma of the vermilion border

seems to be larger. The skin of the back of the hands is now very yellowish thin and pigmented and the underlying fat has practically disappeared. The muscles have atrophied. The knuckles and small joints are very marked. There are not only transverse wrinkles but also longitudinal folds. The hand gives a bony impression.

It should be kept in mind that all signs of ageing are subject to relatively wide variations. However, the evaluation of the appearance of wrinkles is a fairly reliable guide to objective age estimation.

Old age predisposes to a great number of *dermatoses*. Epitheliomas, keratosis, pigmented spots, small hemangiomas, especially the hemangioma of the vermillion border of the lips, xanthelasma of the eyelids, sebaceous adenomas, pendulous fibromas (acrochordon) and other neoplasms are common. The dryness of the skin caused by the reduction of the sebaceous glands is often troublesome. Pruritus senilis is another common and stubborn skin trouble of old age, probably caused by the vascular changes. Purpura senilis (Bateman after Pasini¹⁹¹⁶) is found on the acral and extensor surfaces. On slight trauma or even without it, telangiectatic and purpuric spots appear and undergo the usual color changes leaving long lasting pigmentations. Such spots are often found on the back of the hands where the senile atrophy is pronounced and the exposure to slight trauma is greater than of other parts. Purpura senilis does not disturb the well being of the patient.

Thickening and opacity or dark discoloration of the toe nails is a common sight in old people. The rate of growth of the hair and of the nails is substantially reduced.¹⁹¹⁶

¹⁹¹⁶ Pasini A. Purpura senilis. Monatsh f prakt Dermat 43: 401, 1906.

CHAPTER XXVIII

METABOLIC DISORDERS

Diabetes

The Blood Sugar Test—With the increasing knowledge of diabetes particularly with the development of the methods of blood sugar determination a large number of investigators have studied dermatoses in hyperglycemia as well as the presence of hyperglycemia in dermatoses. Today it is generally held that the absence of sugar in the urine does not rule out diabetes. The determination of the blood sugar level after fasting and after a measured intake of sugar has become an important diagnostic procedure and many investigators have tried to correlate dermatoses and the blood sugar.

The normal fasting values given by different authors vary considerably but 80 to 120 mg. in 100 cc. of blood may be considered normal. The gravimetric methods (Bing, Hagedorn and Jen en) give lower values than the colorimetric methods (John and Wu). Populations with a diet rich in carbohydrates have a higher average blood sugar level than groups whose carbohydrate is lower.¹⁹⁴⁷ For the determination of sugar tolerance some authors prefer the intravenous injection of glucose to the oral administration but today the drinking of 100 grams of dextrose in water after twelve hours of fasting and the determination of the blood sugar after one half, one, two and three hours is a standard method.¹⁹⁴⁸ It not only avoids the intravenous injection but duplicates the normal manner of sugar intake. It must be emphasized that disorders of the endocrine sympathetic system, menstruation, exertion during the test and under or overfeeding with carbohydrate during the days before the test may influence the blood sugar curve. Urbach considers a blood sugar tolerance curve characteristic for diabetes only if

- (1) The highest point of the curve is reached later than one half hour after the ingestion of the sugar.
- (2) If the course of the curve is protracted enough to form a flat curve instead of the normal steep type.
- (3) If the fasting value has not been reached again within three hours.

Blotner¹⁹⁴⁹ considers potential diabetes if the peak of the curve reaches 165 mg. per cent in one half or one hour and he diagnoses diabetes when the blood sugar exceeds 170 mg. and some or all of the urine specimens contain sugar.

Carbohydrate Metabolism in the Skin—Urbach and his collaborators designed a method of examining the skin sugar content which requires only a

¹⁹⁴⁷Urbach, F. *Störungen zu einer physiologischen und pathologischen Chemie der Haut*. Isolierte kutane Glykolyse bei Urach, chronischer Dermatoen. *Med. Klin.* 29: 359-360, 1933.

¹⁹⁴⁸Blotner, H. Glycosuria as a Diagnostic Method in Diabetes. *J. A. M. A.* 133: 1109-1114, 1948.

very small quantity (30 to 40 mg) of skin taken with an electric biopsy punch of 3.5 mm^{1943 1950}

The skin sugar content in laboratory animals varies considerably. In the rabbit it reaches 143 per cent of the blood sugar, the highest of the known values. The normal human fasting skin sugar amounts to only 58 per cent of the blood sugar¹⁹⁶⁰. These findings are remarkable because the blood sugar levels in man and in laboratory animals do not differ greatly, both being between 83 to 111 mg per cent. The *e* figures refer to the so called free sugar. The bound sugar which can be obtained only by acid hydrolysis is fifteen times higher. The skin makes up 16 per cent of the body weight. Only the muscles weigh more of all the organs. Considering the high sugar content together with the fact that the skin weighs one sixth of the body and three times more than the liver, it is apparent that the skin is likely to be important in the sugar metabolism. Urbach¹⁹⁴⁷ considers a fasting skin sugar level of more than 68 mg per cent as pathologic. He showed that the curve obtained by skin sugar determinations after oral administration of 100 grams of dextrose imitates the blood sugar curve but it requires about one half hour more to reach the maximum and about one hour more to reach the fasting value again. Diet low in carbohydrate preceding the test causes a lower fasting level of the skin and blood sugar and a much higher maximum level of the skin and blood sugar curves than a high carbohydrate diet. A diet high in fat lowers the sugar content of the skin while the blood sugar level remains the same¹⁹⁶⁰. In the depancreatized dog the skin sugar increases much more than the blood sugar.

In diabetics the $\frac{\text{skin sugar}}{\text{blood sugar}}$ ratio is high. Following the tolerance test the skin sugar is almost doubled and the time required for return to normal may be longer than five hours¹⁹⁶⁰. This demonstrates that the diabetic skin stores sugar for a long time and would explain its often observed susceptibility to infections. Storage, decomposition and excretion of sugar seems to be a normal function of the skin¹⁹⁵¹.

Urbach found in diabetics with dermatoses such as furunculosis, hyderadenitis, eczema, urticaria and pruritus the skin sugar higher (85 mg per cent) than in diabetics without dermatoses (66 mg per cent) in spite of about equal blood sugar levels. Thus in the diabetics with dermatoses the ratio $\frac{\text{skin sugar}}{\text{blood sugar}}$ seems to be higher than in those without dermatoses. In animals poisoned with extremely high doses of insulin the skin sugar never fell below a certain level. In diabetic patients diet and insulin could not lower the skin sugar below 39 mg per cent. Pillsbury¹⁹⁶ made the existence of an autonomous carbohydrate metabolism in the skin still more evident by studying lactic acid

¹ Urbach & Fanil. De Zu kerg halt der normalen Haut. Biochem. Ztschr. 196 474 1928

² Urbach E. and Lentz J. W. Carbohydrate Metabolism and the Skin. Arch. Dermat. & Syph. 301-316 1945

¹⁹¹ Folin O., Trimble H. C. and Newman L. H. The Distribution and Recovery of Glucose Injected Into Animals. J. Biol. Chem. 75 63-81 1927

¹⁹² Pillsbury D. M. The Intracellular Carbohydrate Metabolism of the Skin. J. A. M. A. 95 428-432 1931

formation in the skin. He found this characteristic product of carbohydrate metabolism to be normally present. The skin contains several enzymes concerned with the splitting of carbohydrates. The stages of this process are the same as in the muscle and in the liver.¹⁰³

Urbach and his associates^{104, 105, 106, 107, 108} discovered what they called *isolated skin diabetes* or *cutaneous glycosidemia*. They found that there exists in some cases a high fasting skin sugar and a flattened skin sugar tolerance curve in the presence of normal fasting blood sugar and a normal blood sugar tolerance curve. The patients suffered mostly from chronic eczema, furunculosis and vaginal or anal pruritus. A certain number of them responded well to insulin and a diet low in carbohydrates, clinically as well as in the fasting skin sugar and in the skin sugar tolerance curve. No transition of skin diabetes into frank diabetes has been observed.¹⁰ Thus, skin diabetes has not become widely known, mainly because of the necessary punch biopsies and the new analytic methods.

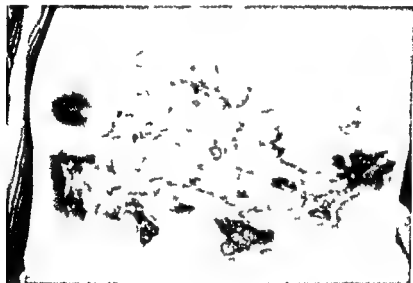


Fig. 10. Skin diabetes with ulcers. Urbach (from Urbach F. *Skin Diabetes Nutritional Metabolism* (Cune & Stratton Inc.))

Besides the excised skin, sweat and serum from artificial blisters have been studied with regard to their sugar content. Urbach emphasizes that the analysis of blister serum is no substitute for that of skin tissue. The blister serum sugar is higher than the skin sugar. Its changes after sugar ingestion are similar but

¹⁰³Wohlgemuth J. *Über den Glykolytstoffwechsel der Haut*. *Deutsch. med. Wchnschr.* 1814 1815 1931.

¹⁰⁴Moncorps C. *Glykolytstoffwechsel und Haut*. *Jahresk. f. Bratl. Fortbild.* 22 7-36 1931.

¹⁰⁵Urbach E. *Isolierte Glykolytämie als Ursache chronischer Furunkulose*. *Zbl.* 41 50^o 1933.

¹⁰⁶Urbach F., Depisch F. and Sacher H. *Über einen hohen Hautzucker bei Hautdiabetes*. *klin. Wchnschr.* 16 45 1937.

¹⁰⁷Urbach F. *Skin Diabetes*. *J. A. M. A.* 129 438-440 1915.

slower than those of the blood sugar^{1959 19 9} In persons who are intolerant to sugar the sweat contains an abnormal amount of sugar After ingestion of much dextrose the sweat sugar may increase 100 to 150 per cent or more even 300 to 400 per cent¹⁹⁶⁰ The sugar from evaporated sweat may accumulate on the skin and cause irritation pruritus and folliculitis just as the sugar does in persons who are occupationally in contact with sugar Carrié and Koenig¹⁹⁶¹ measured the sugar accumulated on the skin It reaches its maximum four days after a bath the armpits collecting more sugar than open areas The sugar on the skin is much higher in diabetics than in normal persons The sweat sugar values determined by reduction only have been considered more recently as being much too high¹⁹⁶

Another approach for testing the skin in diabetes has been advanced by Seelg¹⁹⁶³ Using the method of McClure and Aldrich he compared the time which a wheal produced with 5 c.c. of 1 per cent aqueous glucose solution needed to disappear compared with one produced with 9 per cent saline solution In diabetics and glucose wheals disappeared more quickly yet never before the controls with saline wheals This seems to indicate an increased avidity of the diabetic skin for glucose

The majority of the investigators tried to find out how the blood sugar influences the skin The possibility that the skin or at least pathological changes of the skin might influence the blood sugar has been given much less attention

Skin irritations of many kinds e.g. from croton oil¹⁹⁶⁴ injections of saline foreign proteins and olive oil increase the blood sugar within certain limits according to the intensity of the inflammation^{1964 1965 1968} The extract of artificially inflamed skin injected into normal rabbits raises the blood sugar level to a larger extent than extracts of normal skin The increase is higher in rabbits with already inflamed skin than in rabbits with normal skin It is interesting that high blood sugar curves in psoriasis may become normal after the skin symptoms have been cleared by local treatment¹⁹⁶⁹ Marchionini and

¹⁹⁶⁸Ferrari A V Raffronto fra il contenuto in glucosio del sangue e di liquido di bolla dopo la somministrazione di zucchero per via orale ad individui normali Dermosiflografo 6 293 314 1961 Zbl 38 76

¹⁹Pronzini M La funzione reattiva in alcuni dermatopati Arch Ital di Dermat 12 7 85-81 1931 Zbl 28 764

¹⁹⁶³Lebe H and Habinowitz I M Ecretion of Sugar in Sweat Arch Dermat & Syph 15 706 713 19 7

¹⁹Carrié C and Koenig H Leber den Zuckergehalt auf der Haut bei Normalen und Diabetikern Arch f Dermat u Syph 173 611 614 1936

¹⁹Schulze W Sugar Content of Skin and Sweat Comparative Study of Diabetic and Non-diabetic Subject A J Dermat u Syph 161 471-475 1940

¹⁹⁶³Seelg F F Diabetic Diagnosis I Intradermal Skin Tests Guys Hosp Rep 88 210-217 1938

¹⁹⁴¹Cussen L Effect of Irradiation With Monochromatic Light on Blood Sugar and Lactic Acid in Rabbits Monatsschr 272 354-358 1934

¹⁹⁶³Ayrton G Jr Glucose Tolerance Reactions III Eczema Arch Dermat & Syph 11 627 636 19 5

¹⁹⁶⁴Naraiara A Experimental Studies on Skin Sugar Jap J Dermat u Urol 20 1113 1128 1930 22 87 101 1932 634-653 193 340-366 1932 Zbl 38 765 42 161 43 511

¹⁹⁶⁷Miyak I Einfluss von Dermatitis-Hautextrakt auf Blutzucker Jap J Dermat u Urol 11 1309-1370 1931 Zbl 46 303

¹⁹⁶⁸Marchionini A and Höfner H Ultravioletbestrahlung und Kohlenhydratstoffwechsel Klin. Wochenschr 14 1347 1350 1935

¹⁹⁶⁹Moncorp H Bohnstedt R M and Schmid R Sugar and Glutathione Content of Skin Arch f Dermat u Syph 189 67 76 1933

Hövelborn¹⁰⁰ studied the influence of ultraviolet light on the carbohydrate metabolism. At the height of the erythema the fasting value of the blood sugar drops and the blood pressure decreases. This together with the increase of blood diastase points to one or several insulin-resembling¹⁰¹ substances in the skin produced either in the skin or in the pancreas on stimulation from the skin. Moncorps¹⁰² also found a substance in the skin which raises the blood sugar.

Incidence of Dermatoses in Large Groups of Diabetics.—Greenwood¹⁰³ compared the skin of 500 diabetic and 500 nondiabetic general hospital patients. About 25 per cent of the diabetics either had or had had skin diseases: mainly pruritus (7 per cent), eczema, epidermophytosis, furunculosis and carbuncle (2 per cent) and xanthoma palpebrarum (18 per cent). The patients with a dry skin (20 per cent) seemed to be more apt to develop dermatoses than those with a moist skin. The figures were generally higher than in the nondiabetic group. The total percentages in the control group are meaningless because of the difficulty to obtain reliable figures for epidermophytosis. Tauber¹⁰⁴ found among 514 diabetics, most of whom were hospital patients, gangrene in 18 per cent, ulcers in 4.3 per cent, furuncles and carbuncles in 3.8 per cent, infected hands and feet in 2.3 per cent and pruritus vulvae et ani in 0.8 per cent. This and other lists show that the recorded incidences vary widely even in large groups, probably due to the selection of the studied series. Statistics of hospitalized diabetics are apt to carry a high percentage of severe complications, especially gangrene which is much rarer in ambulatory groups (Lane's series given in Greenwood¹⁰⁵).

How often is a dermatosis the presenting symptom of diabetes? Every experienced dermatologist will remember with satisfaction the cases of perioral eczema, balanitis or pruritus in which he first made the diagnosis of an underlying diabetes. In the large material of the Berlin University Skin Clinic 27 out of 1 000 patients were diabetics and only 13 per cent of them knew of their disease. In the others their diabetes was diagnosed by the dermatologist. Among the diabetic skin patients of the Berlin Clinic 59 per cent had eczema (one fifth of these eczema of the genital region) and 22 per cent balanitis. These patients represent a group with uncontrolled diabetes.

The degree of control of the diabetes is probably the main factor which influences the incidence of dermatoses. The whole dermatological aspect of diabetes has changed since the introduction of insulin. In examining about 200 diabetic patients, most of whom were well controlled, the author was surprised to see how rare were even those skin diseases which are generally considered typical of diabetes. Epidermophytosis was seen to be neither more common nor more severe than in nondiabetics. Gangrene, furunculosis and carbuncle were rare, about 1 per cent. The most common skin change in the controlled diabetic is a slight yellow discoloration, probably due to minor degrees of carotenemia (*Xanthosis diabeticorum*).

¹⁰⁰Greenwood A. M. Skin in Diabetes. 60 Cases. J. A. M. A. 89: 774-778, 1927.

¹⁰¹Tauber E. B. Hyperglycemia in Diseases of the Skin. Arch. Dermat. & Syph. 27: 165-165, 1923.

Mycoses—Greenwood¹⁷⁰ found epidermophytosis in 40 per cent of his series of 500 diabetics. Greenwood and Rockwood¹⁷¹ found clinical evidence of fungus infection in the interdigital spaces of the feet in 70 per cent of diabetic patients, their diabetes being generally uncontrolled. All thickened and opaque



Fig. 47—Epidermophytosis in a diabetic patient

nails were found to be infected. No relationship to the blood sugar level could be established. Percentages of other authors vary widely (see table in Gray and Close¹⁷²). Because of the great differences in the incidence in normal control groups, it is difficult to state whether the incidence in diabetics is actually higher than in comparable normal groups. Many authors¹⁷³ emphasize the importance of the nails as a source of reinfection.

The importance of *mycotic foot infections* in diabetics lies in the danger of more severe infections, complications and gangrene. The clinical aspect of epidermophytosis in diabetics does not seem to have special features.

Every dermatologist has seen in obese women the characteristic though not very common picture of intertriginous genito-inguinal and inframammary dermatitis often caused by *monilia*. This bright red sharply bordered intertrigo surrounded by small pustular satellites is very suggestive of diabetes. Oral moniliasis (thrush) is common in infants but is rare in adults. If it occurs, urine

¹⁷⁰Greenwood A. M. and Rockwood E. M. Skin in Diabetic Patients. Arch. Dermat. & Syph. 21: 95-107, 1930.

¹⁷¹Gray H. and Close W. E. Chiropody and Diabetes. M. Rec. 184: 445-449, 1941.

¹⁷²Kelly H. J. Significance of Dermatophytosis (Cause of Gangrene). Pennsylvania M. J. 31: 531-536, 1933.



Fig. 910. Orlow-Habets: Eritrig on the lateral feet & of the groin

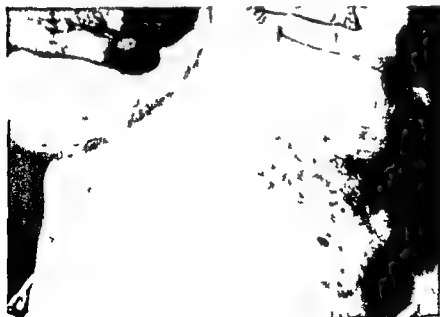


Fig. 911. Orlow-Habets: Eritrig on the lateral feet & of the groin



Fig 20 - Inframammary moniliasis in an obese diabetic woman age 10 years



Fig 21 - Interdigital candidiasis in a diabetic woman

and blood should be examined for sugar.¹⁹⁷⁵ Yeast infections of the hands, feet and particularly of the vulva occur mostly in uncontrolled diabetics.¹⁹⁷⁶ Proper management of the diabetes without local treatment can control the infection. This indicates the specific influence of the diabetes.



Fig. 25. Monilia of the vulva. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

Diabetic vulvovaginitis is usually a mycotic infection.^{1977, 1978} It is encountered in about 50 per cent of women with diabetes. The vulva appears slightly swollen and tender, with a reddish blue color and a thin grayish surface. Abrasions and excoriations, together with a sensation of heat cause much discomfort. The inflammation is usually limited to the moist surfaces, but may extend to the mons

¹⁹⁷⁵Christoph. Soor und Diabetes. Zbl. 22, 606, 1937.

¹⁹⁷⁶Traut H. F., White L. and Hemphill R. B. Monilia of the skin in Diabetes. J. A. M. A. 102, 1290-1292, 1934.

¹⁹⁷⁷Hesseltine H. C. Diabetic or Mycotic Vulvovaginitis. J. A. M. A. 100, 177-178, 1933.

¹⁹⁷⁸Hesseltine and Campbell. Diabetic or Mycotic Vulvovaginitis. Am. J. Obst. & Gynec. 28, 272-283, 1938.

veneris anus and crural folds. Small white areas (thrush spots) on the labia minora contain yeasts. Glucose applied in powder or solution is supposed to cause a flaring up of the vulvitis in mycotic infections as compared with vulvitis of other causes. Hesseltine¹⁹⁷⁷ speaks of mycotic vulvitis rather than of diabetic vulvitis because it is not the irritation from the sugar containing urine but the infection that causes the vulvitis. The sugar fermenting yeast of course finds a good medium in the glucose containing urine and tissues. Optimal growth of yeasts and also of staphylococci is found on media with 150 to 200 mg per cent of sugar. This figure corresponds well to the sugar contents of serum in many diabetics.¹⁹⁷⁸

Diabetes was the cause in 26 of 31 consecutive patients with pruritus vulvae.¹⁹⁷⁹ Fifteen of these 26 diabetics failed to show sugar in the urine. Only blood sugar tests and a detailed history established the diagnosis. These women were between thirty and fifty years of age. Such cases may often be treated as menopausal pruritus if no finer diagnostic test than the unreliable urine test is used.



FIG. 3.—Diabetic balanitis and ulcer of glans penis. (From Urbach E. Skin Diseases Nutrition and Metabolism Grune & Stratton Inc.)

Diabetic balanitis is much rarer than vulvitis the ratio being 1:3.¹⁹⁸⁰ It occurs less often in circumcised men whose glans penis is dry and does not give the yeasts such a favorable moist medium. Among 147 cases of diabetic balanitis treated in the University Skin Clinic in Berlin there was not one in a circumcised man.

Eczema surrounding any not only the urethral and anal orifices is always suggestive of diabetes. Eczema around the eyes may be caused by sugar containing tears perioral eczema and perlèche by sugar containing saliva.

¹⁹⁷⁷Engelhardt W. Haben die beim Diabetiker gehäuft auftretenden Infektionen durch Staphylokokken und Hefen ihre Ursache in dem erhöhten Haut- und Schweisszucker? Münch. med. Wchnschr. 80: 637-638 1933.

¹⁹⁷⁸Jaichöfer A. Hautkrankheiten und Diabetes mellitus. Inaug. Diss. Berlin 1935.

Vascular Disease.—Vascular disease of slight degree is extremely frequent in elderly and middle-aged diabetics. Abnormally low temperature, pallor or cyanosis of the feet have been observed in approximately one-half of 124 patients.^{102,103} The capillary fragility of diabetics is demonstrated by the tourniquet test, is greater at each decade than in nondiabetic groups.¹⁰² Gottron emphasizes the increased capillary reactivity in diabetes.

In many cases gangrene of the toe or foot can be traced to minor skin ailments like epidermophytosis, interdigital fissure, ingrown toe nail, infected corns and calluses and small injuries from self-treatment.¹⁰⁴ All these conditions should receive particular attention. Many of them are caused by improper and



Fig. 54 Diabetic ulcer

tight shoes. Systematic foot hygiene in diabetics has been advocated by many physicians having wide experience in the management of diabetes. The institution of special foot clinics in large centers has undoubtedly helped to decrease the number of serious complications.^{103,104}

¹⁰²Valley M. Diabetes Mellitus as Observed in 100 Cases for 10 or More Years. Peripheral Vascular Findings in 50 of These Cases. *Am J Med Sc* 209: 93-9, 1944.

¹⁰³Heasser M. B. Rudy A. And S. H. Heman A. M. Capillary Fragility in Relation to Diabetes, Hypertension and Age. *Arch Int Med* 72: 118, 1944.

¹⁰⁴Jonlin E. J. Treatment of Diabetes. Philadelphia, 1937. Lea & Febiger.

¹⁰⁵Brandaleone H. Standard M. and Hall E. P. Prophylactic Foot Treatment. *Ann Surg* 105: 120-124, 1937.

In these foot clinics the patients are educated to follow a daily morning routine of a warm foot bath without or with little soap followed by an alcohol rub and dusting with boric acid foot powder. They are advised to massage their feet with lanolin at night. Epsom salt should not be used for the foot baths because it makes the skin dry. Commercial corn remedies should not be applied and blisters not opened. The toenails should be clipped properly. Foot exercises consisting of a series of movements of the toes, feet and legs are considered important if any vascular disease is present. All exercises are done six times and if there is a tendency to coldness the exercises should be done twice a day. An important part of the exercise is the alternating raising and hanging down of both legs for three minutes. Contrast baths of the feet are recommended. The patient should begin with 105° F (40.5 C) and change five times to 50° (10°C) keeping the feet one minute in each bath and finishing with the warm bath. He should keep his feet warm with stockings and not with hot water bottles. Expert care should be taken of abnormal toenails, calluses, corns and mycotic infections. Extremely well fitting shoes and comfortable stockings are important. No walking barefoot, no circular garters or bandages and no metal arch supporters are permitted.

Impending gangrene will usually be diagnosed by observing the following signs¹⁹⁴⁶

1 The pulsation of the peripheral arteries especially of the dorsalis pedis. Both sides must be compared. Good pulsation does not preclude gangrene of a toe because a more peripheral part of the artery may be occluded. Absence of pulsation does not always mean impending gangrene because a collateral circulation may develop.

2 If the color of the elevated and dependent extremity remains the same the prognosis is relatively good whether the pulse is palpable or not. Pallor on elevation, slow recoloring on return to horizontal position and purplish discoloration of the dependent extremities means extensive circulatory disturbance. The level of the abnormal discoloration indicates the approximate level of occlusion.

3 The skin temperature is taken with special thermometers or by running the hand (ulnar side) from the thigh to the toes. One should always compare both sides. A gradual fall of the temperature is normal but a sudden change is of the same significance as a level of discoloration.

4 The histamine test consists in scratching through a drop of histamine solution on both sides and on various levels or in intradermal injections. The wheal and flare formation is supposed to be in inverse proportion to the degree of circulatory impairment.

Diabetic gangrene does not occur in the lower extremities only and it is not entirely a disease of old age. Gangrene of many other parts of the body surface are on record. On the face gangrene may at first resemble erysipelas and later turn into a deep slough frequently with a fatal outcome particularly

¹⁹⁴⁶ Rodinsky M.: Infection of the Extremities. Diagnosis and Treatment. Am J Surg 42: 339-349 1953.

ILLUSTRATIONS

3 Telangiectatic pigmentation of the hand, atrophy and urticarial purpura. Echinomeres appear on light trauma or on percussion with rubber tipped hammer.

Necrotosis tipica diabeticorum (Israel, Oppenheim) (Courtesy Dr. L. Babalian)

4 Diabetes. Infected toenail on early stage of gangrene.

4 Diabetes. Three days later gangrene seen. Local red.

5 Female aged 21 year. Xanthoma diabeticorum unusually large lesion. Blood cholesterol 810 mg per cent.

6 Female aged 21 years. Xanthoma diabeticorum.



PLATE IV

if the cheek is involved¹⁹⁸⁶ Loss of lips, ears, and particularly of the nose as well as perforation of the septum and of the palate have often been reported Gangrene of the penis of the vulva and¹⁹⁸⁷ of small and large superficial or deep areas of the skin are known The superficial gangrene which occurs in small patches is called ecthyma Though rarely diabetic gangrene may occur very early in life Trauma plays a role in unusual sites of diabetic gangrene

The treatment of diabetic gangrene is mainly a surgical problem After drying of superficial necroses with subgallate of bismuth or other means the sores should be dressed with ointments containing as much cod liver oil as possible

In every case of beginning or impending gangrene pancreatic extract (Pancreatic hormone Grant or Sharp and Dohme's pancreatic tissue extract) should be given a trial One to 3 c c are given daily or on alternate days Pa dutin another pancreatic enzyme free preparation is given by injection and by mouth Wolffe¹⁹⁸⁸ recently reported 100 cases of gangrene that had received treatment with enzyme free pancreatic extract Eighty eight per cent of the beginning dry gangrene, and sixty three per cent of the more severe cases with not more than two toes involved were healed The majority of these cases were diabetics The pancreas contains a vasodilatory substance which is able to neutralize the rise in blood pressure produced by epinephrine It furthermore aids in fat metabolism by lowering the blood cholesterol and blood phosphatides This substance is not identical with choline nor histamine It may be identical or partly identical with the alcoholic fat and insulin free neutral pancreatic extract Lipocae¹⁹⁸⁹ which lowers lipemia and allows depancreatized insulin treated dogs to survive for longer than two to three months without the feeding of fresh pancreas

Diabetic Ulcer—Trophic ulcer of the foot is not infrequently found associated with diabetes The diabetic ulcer is not different in its appearance from other trophic foot ulcerations It develops most often on the dorsum or the plantar surface of the big toe or at points of increased pressure The patients are often overweight rarely young Besides the care of the obesity exercises to improve the circulation and the topical application of cod liver oil are indicated Well fitting shoes and protection from cold are most important

Pruritus—Pruritus is especially in women¹⁹⁷⁰ such a common diabetic dermadrome that the urine should routinely be tested for sugar in all cases In all stubborn and unexplained cases blood sugar tests should be done More than fifty per cent of the cases of pruritus sine materia show patho glycemie curves¹⁹⁷⁹ Besides the dietary and insulin treatment French authors have

¹⁹⁸⁶Millett J Diabetic Gangrene of Face 2 Fatal Cases J A M A 112 1143 1939

¹⁹⁸⁷Fikin C W W Occurrence of Diabetic Gangrene in an Unusual Location J A M A 102 2187 1934

¹⁹⁸⁸Wolffe J B Pancreatic Extract in Treatment of Gangrene Am J Surg 68 109-116 1939

¹⁹⁸⁹Dragstedt L R Van Prohaska J and Harris H P Substance in Pancreas (a Fat Metabolizing Hormone) Which Promotes Survival and Prevents Liver Changes in Depancreatized Dogs Am J Physiol 117 175-181 1938

¹⁹⁷⁰Campbell G Gordon Relation of Sugar Intolerance to Diseases of the Skin Brit J Dermat 62 297-304 1931

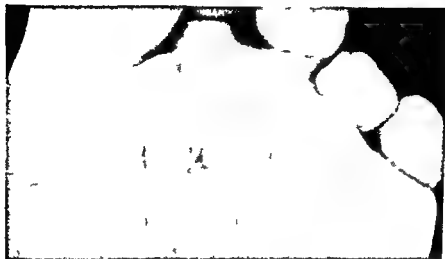


Fig. 56. Uterine hemangioma.



Fig. 57.



Fig. 58.

Fig. 59. Uterine hemangioma.

Fig. 60. Same as after 1 week of diet and inulin treatment.



Fig 8 - F to 11 uncontrolled diabetes



Fig 239 - 1 yod runs in u controlled diab tes

reported successful x-ray therapy to the splanchnic vessels.¹⁰⁰ Spleen extract too has been advocated. Pruritus has been observed not only in hyperglycemia but also in hypoglycemia.¹⁰¹ Cuddeberg and Hannisdal treated such cases successfully with glucose injections and insulin.

Furuncles and Carbuncles have always been considered common in diabetes. This has been statistically confirmed by Greenwood¹⁰² who found the incidence among 500 diabetics about twice as high as the general average of the hospital patients (2 per cent compared with 1.2 per cent) and 7 times higher when furuncles and carbuncles in the history were counted. Williams¹⁰³ who tried to prove that pyogenic infections are no more common in diabetics than in normals, showed that boils and carbuncles occur in 2.3 per cent of hospitalized diabetics. This figure is about four times the percentage of the general hospital average.

Taubert¹⁰⁴ who compared the incidence of furuncles and carbuncles in about 500 hospitalized cases of diabetes with the incidence in 500 patients with normal or rather low blood sugar levels found it to be twice as high among the latter. He also found a diet rich in carbohydrates (Wenckebach's diet), liver extract and daily intravenous injections of 500 c.c. of 5 per cent dextrose solution very helpful. Taubert's¹⁰⁴ figures have so far not been able to destroy the general and deeply rooted opinion that furunculosis is a frequent feature of uncontrolled diabetes.

Stomatitis.—Rudy and Cohen¹⁰⁵ examined the mouths of 403 diabetics, 138 of whom were edentulous. In uncontrolled diabetes particularly if oral hygiene is lacking heavy supra- and subgingival tartar deposits are often formed. Gingivitis, swollen and bleeding gingival papillae and abscesses are common. The teeth which are often decayed become loose but should be saved. The dental condition improves if the diabetes is controlled. No surgical procedure should be done before control of the diabetes.

The tongue in uncontrolled diabetes is often dry and coated. The saliva has been found acid because of the high content of lactic acid. Thrush on the palate and pharyngitis sicca occur.

Pruritus of the Mentus Acusticus is sometimes very annoying and may cause recurrent furunculosis of the external ear.^{106, 107}

¹⁰⁰Gouin F. and Bligny J. A. Traitement des prurits diabétiques et des diabétiques par la radiothérapie sympathique. Bull. Soc. franç. de dermat. et yph. 37-6-3 4 1931.

¹⁰¹Iljarsko J. Pruritus und Pruriginöse Affektionen in ihren Beziehungen zum Kohlehydratstoffwechsel. Acta med. scand. 21: 61-63 1931. 21: 41-44.

¹⁰²Williams J. R. Does Diabetes Mellitus Predispose the Patient to the Pyogenic Skin Infections? J. A. M. A. 118: 1357 1934.

¹⁰³Rudy A. and Cohen M. M. Diabetes Mellitus Oral Aspects. New England J. Med. 219: 603-609 1938.

¹⁰⁴Taubert E. R. Diabetes und Hals- u. n. Ohrenkrankheiten. Wien klin. Wchnschr. 80: 1591 1592 1937.

¹⁰⁵Kecht H. and Dibold H. Relation of Diabetes to Suppurative Conditions in Ear and Nose. Wien klin. Wchnschr. 49: 1341 1343 1936.

Miscellaneous—*Dupuytren's Contracture* of the palmar aponeurosis and Peyronie's disease (induratio penis plastica) either alone or together are rare but have a definite relationship to diabetes. Greenwood mentions the former having a percentage of 1.6 among his 500 diabetics. About twenty per cent of the patients with Peyronie's disease (induratio penis plastica) which often accompanies Dupuytren's contracture are diabetics. Nutritional deficiencies are reported to be more common in diabetes.¹⁹⁹⁷



Fig. 60—Atrophy of subcutaneous fat caused by insulin injection (From Urbach E. *Skin Diseases: Nutrition and Metabolism* Grune & Stratton Inc.)

Fat Atrophy—A peculiar sequel of diabetes is the fat atrophy at the sites of injections of insulin¹⁹⁹⁸⁻¹⁹⁹⁹ which occurs in about 7 per cent of the cases.²⁰⁰⁰ It is a harmless but sometimes disfiguring condition consisting of the localized loss of subcutaneous fat. There is a decided feeling of looseness or emptiness in the subcutaneous tissues. Several such pits the size of a silver dollar may coalesce. Young diabetics with increased basal metabolism are especially inclined to develop this unusual response to insulin. Shelly thinks that the insulin may cause a sudden release of glycogen from the muscle which helps to burn the fat.²⁰⁰¹⁻²⁰⁰² Much rarer than fat atrophy is its opposite, lipoma formation following insulin injections.²⁰⁰³⁻²⁰⁰⁵

¹⁹⁹⁷Rudy A. Unusual Case of Diabetes Disease in a Patient With Diabetes Mellitus. *Endocrinology* 27: 706, 1946.

¹⁹⁹⁸Hoborn C. J. Fat Atrophy From Injection of Insulin. *J. A. M. A.* 87: 1646, 1926.

¹⁹⁹⁹Ditsch F. Lokal Lipodystrophie bei lange Zeit mit Insulin behandelten Fällen von Diabetes. *Klin. Wchnsch.* 8: 1965, 1906.

²⁰⁰⁰Alpert and Ferguson. Local Fat Atrophy After Insulin. *Endocrinology* 33: 741, 1939.

²⁰⁰¹Shelly J. A. Insulin Atrophy (of Fat Tissue). *Pennsylvania M. J.* 49: 347-348, 1937.

²⁰⁰²Winn H. E. B. Diabetes 366 Cases. *J. Iowa M. Soc.* 29: 95-103, 1939.

²⁰⁰³Fret W. Insulin Atrophy of Subcutaneous Fat. *Arch. Dermat. & Syph.* 37: 534-535, 1939.

²⁰⁰⁴Row A. H. and Garrison H. M. Lipodystrophy, Atrophy and Tumefaction of Subcutaneous Tissue Due to Insulin Injections. *J. A. M. A.* 99: 16-18, 1932.

²⁰⁰⁵Gellerstedt N. Zirkumskripte Hyperplasie des subcutanen Fettgewebes als lokale Folge von Insulin Injektion. *Endocrinologia* 33: 417, 1932.

The patient is hypoglycemic shock perspires freely or even excessively while the skin remains dry in diabetic coma.¹⁰⁰

Xanthoma Diabeticorum: A rare condition. Joslin¹⁰¹ observed only six cases among 1 000 cases of severe diabetes. The patients are mostly younger males. The xanthomas appear quite suddenly, usually in large numbers on the extensor surface, the palm and the soles. The individual lesion is a small papule, the size of a pinhead to that of a grain of wheat, rarely larger, red in color with a yellow center which looks purplish but is xanthomatous. They often have an



Fig. 301. Female, aged 72 years. Xanthoma-like lesions on a skin

inflammatory bases and itch moderately. The histology shows intra and extracellular deposit of fat with more inflammation and fibrosis than in primary xanthoma. Ekmann¹⁰² and Mergendanz¹⁰³ classify the diabetic xanthoma with the secondary lipidosis which means they are a complication of a lipemia which can be caused by diabetes as well as by pregnancy, icterus, nephritis or other conditions. The diabetic xanthoma responds to diet and insulin (see also chapter on lipidosis).

Necrobiosis Lipoidica Diabeticorum (Oppenheim & Reich)—It is remarkable that a conspicuous characteristic and not extremely rare dermatosis remained undetected until 1929 when Oppenheim^{104 105} presented a case of a

¹⁰⁰Worli, J. *Comme. Aen. I Insulin Hypoglycemia* JAMA 108: 91, 1933.

¹⁰¹Thannhauser, W. J. and Magrath, H. H. *Diff. reit. Clin. Lab. Group. of Xanthomatous Diseases* 72 *Cas. w. Ann. Int. Med.* 166: 1746, 1938.

¹⁰²Oppenheim, M. *F. i. o. ch. nicht beschrieb. Hauterkrankung bei Diabetes mellitus (Dermatitis atrophica lipoidica diabetica)* Wien klin. Wochenschr. 45: 314-315, 1933.

¹⁰³Oppenheim, M. *F. i. o. ch. nicht beschrieb. mit eigenem Fall ein Beispiel der Degeneration der Haut bei Diabetes mellitus (Dermatitis atrophica lipoidica diabetica)* Arch. f. Dermat. u. Syph. 100: 576-583, 1932.

degenerative skin disease in a diabetic Urbach^{2010 912} in presenting another case three years later emphasized the presence of lipid substances in necrobiotic foci. He related the findings with the disturbance of the fat metabolism in diabetes.

The lesions start as small red papules which grow slowly into irregular plaques from one to several inches in diameter. In their mature stage they are waxy or mottled with a red yellow center. The border is violaceous with a red or brown areola. Subcutaneous nodules may be covered with normal skin. The surface

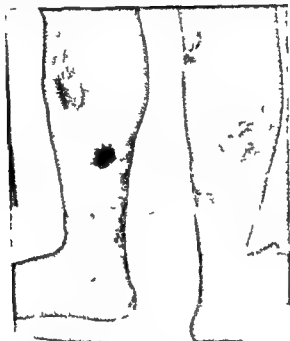


Fig. 11.—Xerosis lipodidea diabetica (Urbach Oppenheim). (From Urbach F. *Skin Diseases Not Hides and Metabolism* Grune & Stratton Inc.)

of the older plaques is usually traversed by fine telangiectatic vessels. The plaques are quite hard especially along the edges. They are not elevated but the center of the lesions is flat or depressed. The surface of the older lesions is shiny as if covered with collodion. There is hardly any scaling. Ulceration of the center may occur. There is a tendency to heal slowly with an atrophic scar but this may take many years.

The average number of lesions runs from a few to a dozen. They are most often located on the lower legs. Lesions on the hands and in other regions have been described but none on the face. Itching or pain is never mentioned tenderness usually being the only complaint.

²⁰¹⁰ Urbach E. Lipidstoffwechselkrankung der Haut. *Handb. d. H. u. C.* 22: 234-34, 1933.

⁹¹² Urbach F. Necrobiosis diabetica. Ein neu diabetisch Stoffwechseldermatos. *Zbl. 41* 64, 1937.

⁹¹³ Urbach F. Eine neue diabetisch Stoffwechseldermatos. Necrobiosis lipodica diabetorum. *Arch. f. Dermat. u. Syph.* 166: 285, 1937.

The histology of necrobiosis lipoidica diabetorum is of great interest. The primary phenomenon seems to be an intense localized angitis. There is an inflammatory thickening of the vascular walls which leads to gradual occlusion of the blood vessels particularly of the small arteries with slow necrosis of the areas involved. The collagenous fibers become waxy and swollen and the nuclei disappear or stain but poorly with eosin. The elastic fibers deteriorate. Hemosiderin is present explaining the brownish hue of the older lesions. The necrobiotic areas become impregnated with fat droplets which lie mostly but not



Fig. 63. Uncontrolled diabetes mellitus: hypertensive hemorrhagic rash.

always extracellularly, sometimes surrounding the vessels in a certain distance.²⁰¹³ Lymph capillaries stuffed with fat have been demonstrated. The droplets stain bright orange red with Sudan III while the necrotic collagen is dull brown. Foam cells in xanthomas, calcium deposits and giant cells have been observed.²⁰¹⁴ mainly in the periphery of older lesions.

²⁰¹³Gotttron H. Dermatitis Atrophicans Lipoides Diabetica. *Med Klin* 31: 143-100, 1934.

²⁰¹⁴Nicholas L. Necrobiosis Lipoidica Diabetorum With Xanthoma Cells (Case With Pulmonary Tuberculosis). *Arch Dermatol & Syph* 48: 606-611, 1913.

Both neutral fats⁶¹⁵ and doubly refractory cholesterol have been demonstrated. High blood lipids, especially cholesterol have frequently been found. The fat in the necrobiotic tissues is probably deposited from the blood.

Ninety of the approximately one hundred cases so far presented were diabetics. There is a preponderance of the female sex.

The usual antidiabetic treatment does not seem to influence the condition but a diet low in fat as advocated in certain xanthomas has been recommended.^{6013 2017}

Diabetic carotenemia or *xanthosis diabetica* (see carotenemia) is probably the most common diabetic dermatome. It has long been considered harmless and explained by the fat and vegetable diet of the patients. Recently Rabinowitch⁶¹⁸ found among 1014 diabetics fifty nine cases of xanthosis thirteen of whom had never been on special diets prior to the detection of this skin condition. The percentage of carotenemia in diabetics is probably much higher when the diagnosis is based on increased serum carotin and not only on clinical discoloration. Being a frequent accompaniment of severe diabetes cardiovascular disease insulin edema resistance to insulin and hypercholesterolemia it suggests an unfavorable prognosis for the diabetes. The disturbance of the lipid metabolism in diabetics the failure to synthesize vitamin A from its precursor carotin and possibly disturbed excretion of the carotin seem responsible for the accumulation of the lipochrome in the body.

The Blood Sugar in Various Dermatoses

The blood sugar has been investigated in all common and many rare dermatoses. Except for the established diabetic dermatomes the results have been meager. In finding a high blood sugar level one should recall that inflammatory processes in the skin are able to raise the blood sugar.²⁰¹⁹ The blood from capillaries of inflamed skin contains more sugar than from normal skin.⁶²⁰

In groups of eczema patients^{1965 1990 2021} a higher percentage of sugar intolerance has often been claimed but also denied.^{1971 622} Dermatitis intertriginosa seems more than other types of eczema correlated to sugar intolerance.⁶²⁴

⁶²¹Zeis E P and Caro M R. Necrobiosis Lipoidica Diabeticorum. Arch. Dermat. 30 796-812 1934

⁶²²Goss P and Machacek G F. Necrobiosis Lipoidica Diabetica. Arch. Dermat. & Syph. 32 401 1935

⁶²³Urbach H. Cutane Lipoidosen. Dermat. Ztschr. 66 371-386 1933

⁶²⁴Rabinowitch I M. Carotinemia and Diabetes. Canad. M. A. J. 18 527-530 1928

⁶²⁵Abraham W. Zur Blutzuckererhöhung der Dermatosen. Dermat. Wchnschr. 91 465-470 1933

⁶²⁶Waldman A and Galla A. Vergleichende Untersuchungen über den Zuckerspiegel in den kapillaren pathologisch veränderten sowie normaler benachbarter Hautbezirke. Dermat. Wchnschr. 34 1255-131 1933

⁶²⁷Allison J R. Hyperglycemia in Skin Diseases. South. M. J. 26 735-742 1937

⁶²⁸Hoffmann E H and Hegerzell H S. Blutzucker und Hautkrankheiten. N. derl. tijdschr. v. Geneesk. 75 3904-39 6 1931. Zbl. 30 376

⁶²⁹Waldman A and Galla A. Abnormalities of Blood Sugar Content in Eczema. Brit. J. Dermat. 37 364-370 1955

Dry skin and *chapping* of the hands in cold weather should call attention to the possibility of a latent diabetes.¹²⁰² Chronic and unexplained eczema of the hands should be reason to search for diabetes.

It is an old experience that sugar and chocolate tend to make *acne* worse and that a diet low in sugar and starches is favorable for this condition. This is in accordance with Rosenfeld's¹²⁰³ findings that sugar in the diet stimulates the secretion of the sebaceous glands more than fat. Schwartz¹²⁰⁴ Highman and Mahankin found high blood sugar levels in fifteen out of about thirty *acne* cases and also a similar percentage in *seborrhea*.¹²⁰⁵ Recently Simon and Herrmann¹²⁰⁶ reported good results in treating *acne* with small doses of insulin.¹²⁰⁷ They refer mainly to cases with menstrual exacerbations, emphasizing that the blood sugar tolerance curve during menstruation is flattened reaching the fasting value more than three hours after the sugar intake. Many authors¹²⁰⁸⁻¹²¹⁰ more or less deny the relationship of *acne* and hyperglycemia. Lately healing of *acne* during hypoglycemic shock therapy of psychoses has been reported.¹²¹¹ A great deal of evidence has been furnished demonstrating hyperglycemia in *psoriasis*.¹²¹² Tulaik was unable to confirm these findings. However there seems to be a relationship between diabetes and *psoriasis* which expresses itself in the occasional coincidence of both conditions in individuals and families. Greenwood¹²¹³ found 2.4 per cent of *psoriasis* among his 500 diabetics. This was ten times the percentage of the control group.

¹²⁰² Host G. A. Hyperglycemia and skin diseases. *Brit. J. Dermat. & Syph.* 55: 5, 1952.

¹²⁰³ Rosenfeld J. O. *Hauttata und Diät*. *Zbl. Ges. Med.* No. 40, 1906.

¹²⁰⁴ Schwartz H. J. Highman W. J. and Mahankin H. C. Sugar Content of the Blood in Various Diseases of the skin. *J. Cutan. Dis.* 31: 159-165, 1916.

¹²⁰⁵ Schwartz H. J. *Dermatolog. in Diabetes*. *Dermatologica* 87: 89-93, 1943.

¹²⁰⁶ Simon A. and Herrmann J. D. III. Sugar Metabolism in Certain Dermatoses Especially in *Acne Vulgaris*. *Arch. Dermat. & Syph.* 26: 1-10, 1932.

CHAPTER XXIX

METABOLIC DISORDERS

Lipidoses

Chemical Data—The following lipids occur in the organism

1 *Sterols* This important group which includes cholesterol and its esters the bile acids the sex hormones and some other organic substances has a characteristic structure with four rings²⁹⁹. Cholesterol is absorbed and synthesized in the body. It is excreted in the bile and partly reabsorbed the larger part being transformed into coprosterol and eliminated with the stools. Cholesterol always accompanies neutral fat.

2 Nitrogen and phosphorus-containing *phosphatides* such as lecithine cephalin sphingomyelin and the cerebroside.

3 The *neutral fats fatty acids* and *soaps*. These form the bulk of the body fat.

Normal (average) values for lipids in the blood serum³⁰⁰

	mg% Plasma		mg% Of total lipids
Total cholesterol	180	(110-150 Windaus) (100-210 Peters and Van Dyke)	34
Cholesterol esters	185	(40-70)	70
Lecithin	225		43
Total fatty acids	345	(190-420) (Peters and Van Dyke)	66
Total lipids	525	(700-800 Schaaf ^{101d}) (570-820 Peters and Van Dyke)	100

Three per cent of the net weight of normal skin is made up of lipids. Five to fifteen per cent of the total lipids is cholesterol. Lecithin varies from only a trace up to 30 per cent of the total lipids.

The lipids in the serum depend on the intake and absorption, the migration, the deposition and disintegration of fat in the system and on the disturbances of the lipid metabolism in the cell³⁰¹.

Pathology and Pathogenesis—Several disturbances of the fat metabolism are accompanied by tumor-like lesions in the skin and in other organs which are called *xanthomas*. While there are vast differences in the clinical appearance and in the severeness of the systemic involvement, the histologic picture of all xanthomas is characterized by the presence of certain characteristic cells which are imbedded in a stroma.

²⁹⁹Thannhauser & J. Lipidoses Oxford Medicine Vol. II VIIA New York 1940 Oxford University Press

³⁰⁰Montgomery H. and Osterberg A. E. Xanthomatosis Arch. Dermat. & Syph. 27 373-402 1933

These cells called foam cells are large at least of epithelium size. They occur mostly in nests but diffuse infiltration to the degree of almost complete substitution of the normal tissue is known. The foam cells are constituents of the reticulo endothelial system (Aschoff and his school (cf. Thannhauser¹⁰¹)). Perivascular reticulum and phagocytic connective tissue cells may become foam cells by being stuffed with fat droplets. In their mature stage they look alike. The foam cells may form giant cells of various types but there are no mitoses. Pigment probably of blood origin is frequently present. Cholesterol esters stain brown with Sudan III and dark blue with Nile blue sulfate. In polarized light they show the cross figures of double refraction.

The conceptions of the pathogenesis of the xanthomas and especially of the origin of the lipids in the foam cells have often changed^{101, 102, 103, 104}. Lillitzer and Wile¹⁰¹ observed that the xanthomatous changes started in the adventitia of the small blood vessels. They concluded that the lipid substances in the xanthoma cells stemmed from extravasated blood and that their presence stimulated the connective tissue of the skin to hyperplastic growth. L. Pick and F. Pinkus¹⁰² however refuted the idea of hyperplasia or tumor formation. They suggested that the cholesterol infiltration of the cell was caused by the hypercholesterolemia which is often associated with xanthoma formation. However xanthoma arises without hypercholesterolemia and the frequent hypercholesterolemia in diabetes, icterus, renal disease and pregnancy without xanthoma formation made it probable that hypercholesterolemia was not the only source of the fat in the foam cells. Aschoff and his school (lit. see Thannhauser¹⁰³) demonstrated that *only the cells of the reticulo endothelial system could become xanthoma cells*. Another advance was the *chemical identification* of the lipid in the various forms of lipidoses with cholesterol dominating in the xanthomas^{102, 104}. L. Pick¹⁰² interpreted xanthoma formation as a storage disease. The fat droplets which were taken up and stored like vital dyes by the cells of the reticulo endothelial system apparently could not be disintegrated in the intermediary metabolism.

The decomposition of the blood lipids in the light of colloid chemistry is the center of the xanthoma theory of Bloch, Schraff and Werner^{104, 105} propounded later especially by Schraff¹⁰⁵.

These authors emphasized the importance of the *ratio of the lipid constituents* in the blood and in the tissues (free and bound cholesterol, phosphatides, true fats and perhaps other compounds as well). A change of the ratio of the lipid fractions would disturb the equilibrium of the lipid emulsion of the serum and lead to coarsening of the lipid particles in the emulsion to decomposition and

¹⁰¹Lillitzer S. and Wile U. Xanthoma Tuberorum Multiplex J. Cutan Dis. 30: 35-41 1911

¹⁰²Pick L. and Pinkus F. Über doppelthrebbende Substanzi Hauttumoren etc. Monatschr. prakt. Dermat. 5: 46 1904

¹⁰³Pick L. Classification of Diseases of Lipid Metabolism and Gaucher's Disease. Am. J. Med. Sc. 193: 453-469 1933

¹⁰⁴Bloch H. Metabolism Failure. Clinics and Skin Diseases. Special Reference to Acne Vulgaris and Xanthoma. Brit. J. Dermat. 43: 61 1951

¹⁰⁵Schraff F. and Werner A. J. Die Pathogenese der Xanthome. Die Beziehungen von Cholesterin, Phosphatid und Gesamtstoffgehalt des Blutes zur Entstehung der Xanthome. Arch. f. Derm. t. 162: 217-230 1910

precipitation of individual constituents in the tissues and finally to xanthomatous lesions. It was suggested¹⁴¹⁸ that the regulation of the concentration of fat emulsifying agents is a particular liver function the disturbance of which causes an impairment of the colloidal dispersion of fats in the blood serum and an increased tendency to throw the fats out of the emulsion. Local contributory factors may modify the distribution of the xanthomas which develop in reaction to the deposits of de emulsified fats. After formation of xanthomas the metabolic disturbance may subside leaving the xanthomas. In such cases xanthomas without symptoms of disturbed fat metabolism may be encountered.

Schaaf's conception was based on Spranger's¹⁴¹⁹ investigations of emulsions. A fat in water emulsion is stable only if the concentrations of emulsifying agents are present in a definite ratio to each other. Only under these optimal conditions can the fat droplets remain in the finest possible state of dispersion. Every variation in this ratio increases the readiness with which the fat separates from the water. Cholesterol, cholesterol esters and the phosphatides play an important role in the emulsification of fat in water. In Ringer's solution containing proteins in quantities corresponding to those in the blood serum optimal distribution of neutral fat in the presence of cholesterol and cholesterol esters takes place only if this mixture of emulsifying agents contains 60 per cent cholesterol esters. In normal blood serum 60 to 70 per cent of the total cholesterol is present in the form of cholesterol esters. This fact stands in striking agreement with the optimal concentration of these two emulsifying agents.

The ratio may also be changed by local factors such as trauma and inflammation. Schaaf's conception of xanthoma formation is further based on the experimental production of xanthomas in animals. Xanthoma formation in patients with a normal total fat content or a normal total cholesterol content is explained by the assumption of an abnormal ratio between the emulsifying agents especially cholesterol and cholesterol esters, phosphatides, neutral fats and fatty acids. The absence of xanthomas in hyperlipemia or hypercholesterolemia can be explained by the stability of the colloidal system in spite of the total increase of lipids due to the correct ratio of the constituents.

Montgomery¹⁴²⁰ recently reemphasized the old experience that cutaneous xanthomas are not uncommonly seen in association with hepatic disease especially obstructive jaundice. (See Xanthomas.)

Thannhauser and Magendanz¹⁴²¹ and Thannhauser¹⁴²² emphasized and proved again with a great array of evidence both chemical and clinical that the specific lipids which form the cellular deposits are only in some cases present in excessive amounts in the blood serum. They claimed that there is no proof of a colloidal decomposition of the serum or of the cell fluids resulting in precipitation which was the prerequisite of the hypothesis.

They concluded that in one group of lipidoses which they called primary lipidoses the cause must be an intracellular disturbance of the lipid metabolism. The fat droplets in the cells are in their opinion not supplied by the

¹⁴¹⁸Spranger W. Zu physikalischen Gesetzen der Körperflüssigkeiten. Ein Beitrag zur Physiologie der Verwertung. Bloch u. Züscher 208: 164-178, 1919.

¹⁴²⁰Montgomery H. Xanthomatosis. J. Invest. Dermat. 1: 3, 5-351, 1934.

blood stream but formed and retained within the cell in the presence or absence of hyperlipemia. This theory found important support in the observation that *tissue cultures of xanthomas* are able to develop doubly refractile substances.²³¹ The primary lipidoses are often hereditary. Thannhauser and Magendanz²³² did not deny that hyperlipemia may cause xanthomas. Xanthomas in hyperlipemia of which the diabetic xanthoma is the best known type were grouped together as secondary or hyperlipemic xanthomatoses.

Xanthomas

The cutaneous xanthomas are either solitary, localized in a few areas or scattered over the body surface. The solitary xanthoma is represented mainly by the eyelid xanthoma (xanthelasma) which is almost always flat (Xanthoma planum). Xanthomas in other regions are usually prominent either papular or tubercous (Xanthoma tuberosum multiplex). The xanthomas which are scattered over the body are mainly discrete shotty papules (Xanthoma disseminatum) which sometimes form large tubercous plaques.

Xanthoma planum palpebrarum (often called xanthelasma) is the only common type of xanthoma. All the others are rare conditions. It forms a single or more often a small number of oblong soft flat hardly prominent light yellow plaques. They surround the inner canthus in an arc which extends to the upper and lower lids. Rare atypical lesions may be red, brown or white, hard or tubercous. The author saw a case of xanthoma palpebrarum with tubercous nodules the size of a hazelnut so that the vision became disturbed.

The lid xanthomas appear mostly in the fifth and sixth decades.

The common and reputedly harmless but popularly and medically suspected xanthoma palpebrarum did not prove so insignificant as often believed. Montgomery²³³ studied 38 cases. More than 20 per cent had serious cardiovascular disease, hypertension, coronary sclerosis or angina pectoris. There was a definite increase in one or more of the blood lipids²³⁴ and a consistent increase in lecithin. Montgomery²³⁵ concluded that xanthoma palpebrarum is an accompaniment of systemic disease and that the condition is simply a variation of one of the types of xanthoma. Polano²³⁶ found high or otherwise abnormal blood lipids in 25 per cent of the eyelid xanthomas. Thannhauser and Magendanz²³⁷ call forme fruste of essential xanthomatosis a condition in which slight xanthoma of the lids, dark pigmentation around the eyes and xanthosis of the skin due to carotenemia are the only (and inconstant) dermatomes. However, there is a high blood cholesterol and a low basal metabolism. Diabetes and signs of angina pectoris are not infrequent findings. The incidence of eyelid xanthomas in middle aged lepers (10 per cent) is more than ten times higher than normal. It can be explained by high blood cholesterol and leprous involvement of the liver which is encountered in almost all necropsies.

²³¹Hiederman W. & Hoefler I. Züchtung von xanthomgewebe in vitro Arch. f. exper. Zellforsch. 10: 1930.

²³²Curti A. M. and Berg J. P. Effect of Feeding a Lipotropic Substance to Patients With Xanthelasma Arch. Dermat. & Syph. 125: 56, 1943.

²³³Polano M. J. Die Xanthelasmatose und Haut Arch. f. Dermat. u. Syph. 181: 139-12, 1940.



Fig 264



Fig 265



Fig 266



Fig 267

Fig 264 — Xanthoma tuberosum multiplex — com disseminated papules (Courtesy Division of Dermatology Department of Medicine University of Chicago)

Figs 265-267 — Xanthoma (Courtesy Division of Dermatology Department of Medicine University of Chicago)

Xanthoma Tuberosum Multiplex and Xanthoma Disseminatum—A tendency to form lines, stripes or oblong arrangements is a peculiarity of both the xanthoma palpebrarum and the disseminated types.²³⁰ Multiple xanthomas in small numbers (xanthoma tuberosum) are typically localized on the extensor surfaces of the elbows, the knees and the heels. These xanthomas except those of the palms are rarely as flat as those of the eyelid. Papular, tubercular or lobulated forms on flat bases or short peduncles occur. The individual xanthomas may be crowded in ridges or furrowed plaques which may cover an entire nail.²³¹ The xanthomas in the neighborhood of joints and tendons may be very firm, originating in the tendons or tendon sheaths, and may become adherent to the bones. The variety of features and the transitional types show that a sharp anatomical distinction between localized and multiple, and also between flat and tubercular xanthomas is not possible.



FIG. 64. Xanthoma tuberosum multiplex (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

Montgomery studied 26 cases of xanthoma tuberosum. High blood cholesterol, familial histories and early coronary (27 per cent) or other forms of severe vascular disease (46 per cent) were though not constant surprisingly frequent features. The combination of xanthoma tuberosum of the extensor surfaces with occlusive arterial disease is known since at least 1873 (Fugge after Thrombhauser²⁰⁹ and Barker²⁰⁴).

²³⁰Wiss, F. and Garl, J. Xanthoma Dissectorum With Unusual Form of Eruption. Arch. Dermat. & Syph. 45: 723-737, 1947.

²³¹Barker, W. Occlusive Arterial Disease of Lower Extremities Associated With Lipemia and Xanthoma Tuberosum. Ann. Int. Med. 12: 1801-1939.

The rare *disseminate xanthoma* is characterized by an abundance of small papular, shotty lesions and plaques. This type favors the flexor surfaces but may involve the entire skin. Involvement of the sclerae and of the upper air passages occurs.

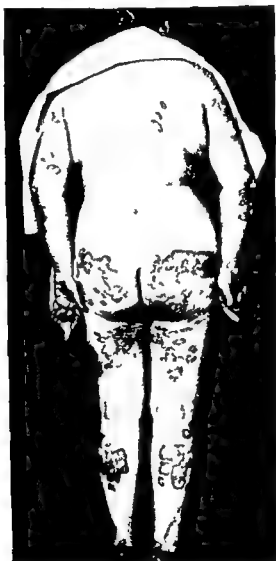


Fig. 209.—Xanthoma tuberosum multiplex. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

Herrmann and Nathan¹⁹²² described very thoroughly (1926) two cases of xanthomatosis. In one case small xanthomas were disseminated over the whole body surface and the blood cholesterol was normal. In the other case the

¹⁹²²Herrmann, F. and Nathan, F. Zur Frage der Xanthomatosen. Arch. f. Dermat. u. Syph. 183: 575-601, 1926.

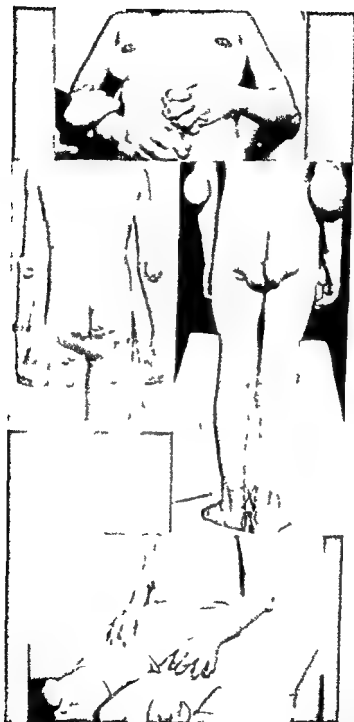


Fig. 270 -- Four siblings affected with tuberous xanthomatosis of the extensor type. Father who had high blood cholesterol married a second cousin. Of the children 3 were xanthomatous. One of the other children suffered from cardiac disease and had like another non-xanthomatous child high blood cholesterol. (From Bloom D. Kaufman, R. and Stein H. A. Arch. Dermat. & Syph. 194)

xanthomas were tuberous and limited to the extensor surfaces of the knees and elbows to the extensor tendons of the fingers and to both Achilles tendons. The blood cholesterol was high — a brother of the patient had hypercholesterolemia without xanthomas. The authors emphasized that the two cases represented *two clinically and pathogenetically different types of xanthomatosis*.

More recently Polano⁶⁶⁰ Thannhauser and Magendantz⁶⁶⁷ Montgomery and Osterberg⁶²⁰ and other writers investigated the features of the two types. Tuberous xanthomas of the extensor surfaces in moderate number appearing early in life, involvement of the tendons and tendon sheaths, cardiovascular and liver disease, high blood lipids and dominant heredity characterize one type. Disseminate abundant small nodular xanthomas with predilection for the flexor surfaces, involvement of the brain and nerve tissue causing diabetes insipidus and invasion of the bones, larynx, lungs and lymph nodes feature the

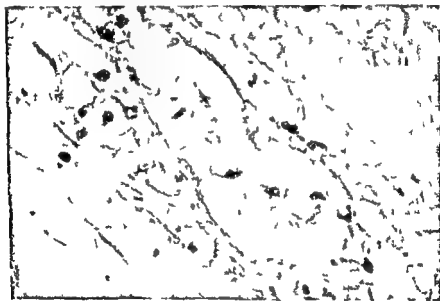


Fig. 971 — II nodular xanthomatous. Foam cells in a lipid deposit in the aorta. (From Bloom, H. J., and Haufman, S. R. *Quintessence of Medicine*, 1944, p. 194.)

other type. There is no jaundice. These cases of the disseminate type usually have normal or high normal blood cholesterol. The prognosis is particularly bad if the air passages are involved, which may necessitate tracheotomy. Thannhauser and Magendantz⁶⁶⁷ emphasize that they were not able to find a single case described in which disseminate xanthoma was found combined with endocardial and vascular xanthoma. The situation is quite different in the extensor type. The xanthomatous involvement of the endocardium, the valves and the large vessels, particularly the aorta, is the cause of the sudden deaths which occur very strikingly in the xanthoma families. The case of Arning is particularly well known. The mother and five out of nine children had xanthomas. Three of

the children died at the ages of 16, 21 and 26 years of sudden heart attacks, two of them while dining. Similar dramatic fatalities have been reported repeatedly.²⁹⁴ The exhaustive necropsy findings in such a case have recently been published by Siegmund.²⁹⁵ A girl of six years had been showing xanthomatous tuberosi of the extensor surfaces of the buttocks and of the eyelids since the age of 18 months. Gradually the girl grew weaker and died from circulatory collapse. The heart valves, the root of the aorta and the coronary arteries showed lemon yellow xanthomas with cholesterol and calcium deposits. There was central congestion and atrophy of the liver, but the Kupffer cells were free of fat. The kidneys showed xanthomas in the papillae. It is remarkable that the reticulo-endothelial system was free of fat. Two years later a brother 11 years old died suddenly. The post mortem findings were almost identical and so were those in one of the 5 stunted siblings in the case of Bloom, Kaufman and Stevens.²⁹⁶

Liver disease was found connected with xanthomas early in 1850 by Addison and Cull.²⁹⁷ Montgomery²⁹⁷ demonstrated hepatic disease particularly obstructive jaundice in 8 out of 55 xanthoma cases. Xanthomatosis in icterus following neoplasmin treatment has been seen in several instances.²⁹⁷⁻²⁹⁹ Biliary cirrhosis is apt to be seen with cutaneous xanthomas of the flexor surfaces. The cause of the obstructive jaundice is often found in xanthomatous changes of the bile ducts.²⁹⁹

Hyperlipemia is present in tuberosus xanthoma but the normal ratio between cholesterol and cholesterol esters frequently remains undisturbed. Its inversion proves severe liver damage.²⁹⁹ Phosphatides (lecithin) are likely to occur. In many cases of hepatic disease associated with cutaneous xanthoma in other locations than in the eyelid, palmar lesions can be found. The eyelid xanthomas in jaundiced patients often look lighter than the neighboring skin.

Cutaneous xanthomas may undergo involution as the condition of the liver improves. Thinnhauser and Magendantz³⁰² point out that frequently the cause of the liver disease in tuberosus xanthoma is a xanthomatous biliary cirrhosis. Enlarged liver and spleen with jaundice of years duration, hypercholesteremia with inverse ratio of cholesterol/cholesterol esters together with xanthomatous tuberosi and plana of the extensor surfaces and buttocks are a characteristic diagnostic triad. If xanthomas of the tendon sheaths and tuberosus xanthomas of the skin exist over a long time without jaundice, involvement of the liver is rare.

In cases of biliary cirrhosis caused by xanthomatous involvement of the liver an eruptive, universal papulopustular form of xanthoma was seen which in con-

²⁹⁴Bloom D, Kaufman H and Steiner R A. Hereditary Xanthomatosis. Familial Incidence of Xanthoma Tuberosum With Hypercholesterolemia and Cardiovascular Involvement. Quoted in Dathin & Verel. *Cas. Arch. Dermat. & Syph.* 48: 115, 1947.

²⁹⁵Siegmund H. Familio-vasculäre Xanthomatose als Todesursache bei jugendlichen Müttern. *med. Wchnschr.* 88: 1617-1619, 1974.

²⁹⁶Addison and Cull. On a certain Affection of the Skin. *Virchow's* 11a (a) Plana (b) Tuberosa. *Guys Hosp. Rep.* 2nd series vol 7 p. 64, 1851.

²⁹⁷Fulcher and Stoke. Multiple Xanthoma. *Arch. Dermat. & Syph.* 27: 337-349, 1933.

²⁹⁸Nohl G. Formen der generalisierten Xanthomatose. *Dermat. Wchnschr.* 84: 877-883, 1937.

trast to xanthoma without liver involvement was extremely itchy. The soft small papules were scratched so that a prurigo like picture resulted.

The multiple forms have been encountered early in life in many cases in childhood. Urbach emphasizes that in childhood the fresh papular lesions are often bright red and not yellow due to the more abundant vascularization of the infantile skin. The xanthomas rarely heal spontaneously.

Hand-Schuller-Christian's Disease is a syndrome related to the xanthomatoses. It is characterized by the triad: defects in the flat bones of the skull, exophthalmus and diabetes insipidus.⁶⁴⁰ Rowland⁶⁴¹ recognized the lesions of this disease as a special type of xanthomatosis with lipid storage in many parts of the reticulo-endothelial system. The infrequent involvement of the skin is surprising in this syndrome in view of the particular affinity for the skin in the other forms of xanthomatosis. There are on record some cases with eczematous or purpuric yellow or red brown widespread papular rashes. A few developed xanthomata palpebrarum and disseminata. In one of the cases⁶⁴¹ the lenticular dermal xanthomas occurred in great profusion about the mouth and neck and the flexures of the big joints. On the penis they were so numerous that a phimosis resulted. Purpura may precede the xanthomas. In the eczematous lesions of one case foam cells were found.⁶ Gottron²⁰⁴ interprets the Hand-Schuller-Christian dermatosis as a primary granulomatosis with secondary lipid deposits in the later stages. This closely follows the conception of Chester⁶⁴² who considered the granulomatous changes as the primary trouble and the lipid infiltration as secondary in the disorder. Hypercholesterolemia has often been found.

Secondary Xanthoma—(Xanthoma diabeticorum etc.) Thannhauser and Magendanz²⁰⁸⁷ emphasize that the eruptive form of xanthoma (xanthoma diabeticorum) is etiologically entirely different from all xanthomas due to primary xanthomatosis. It is a symptom of lipemia and may occur in diabetic lipemia as well as in lipemia associated with other diseases. It has been observed in cholesterolemia due to icterus, pregnancy or nephritis. The difference between primary and secondary xanthoma is well illustrated by the rare cases of combination of both. In these cases the eruptive lesions disappeared under dietary treatment but the tuberous primary xanthomata remained.

The eruptive subacute transitory and inflammatory character is the main distinguishing feature of the secondary xanthomas of which *xanthoma diabeticorum* is the best known (see diabetes).

Treatment of Lipidosis—According to Thannhauser and others the normocholesterolemic type does not respond to dietary treatment. The case

Christian H. A. Defects in Membranous Bones, Exophthalmus and Diabetes Insipidus. Contribution to Medical and Biological Research, vol. I, New York, 1919. (a) H. Hoerber, loc. cit. p. 390.

⁶⁴⁰ Rowland H. G. Cholesterol Syndrome and Lipoid Cells. Hyperlipemia of the Reticulo-Endothelial System. *Ann. Int. Med.* 2: 1-14, 1929.

⁶⁴¹ Gottron H. Schüller-Christian Syndrome. *Arch. f. Dermat. u. Syph.* 182: 681-731, 1931.

⁶⁴² Wagner H. Die Späterkrankheiten (Thesaurismosen). *Fortschr. d. inn. Med. u. Kinderh.* 53: 56, 1933.

⁶ Chester W. L. Hyperlipid Granulomatose. *Michigan Arch. f. Path. Anat.* 279: 561-60, 1930.

associated with hypercholesterolemia may respond to a diet low in cholesterol. Such a diet is mainly vegetarian, no animal fats being permitted.

Lipocain is a defatted alcoholic pancreatic extract studied by I. R. Drigstedt. It seems to contain a hormone which influences high lipid values in the blood and it should be tried in hypercholesterolemia, xanthomatosis.

Diabetic xanthoma responds quite readily to diet and insulin. The diet should avoid too much fat, particularly animal fat.

A trial should be given to the treatment of xanthomatosis with ultraviolet rays. The effects seem to be of a general nature exceeding the radiated area.¹⁹⁴ X-ray treatment is locally effective in the tumors of Hand-Schüller-Christian's disease, rarely in other xanthomas. The eyelid xanthomas may be treated locally.

A few very rare diseases which are interpreted as lipidoses may be mentioned briefly.



Fig. 27. *Lipoidosis cutis et mucosae* (lipid proteinosis) (Urbach-Wiethe). (Courtesy Dr. Erich Urbach.)

Extracellular-Cholesterinosis (Kerl-Urbach).—This is a chronic disease coming on over many years. Maculopapular coalescent violaceous indistinct lesions and disseminated yellowish nodules are seen on the trunk. In addition there are tuberous tumor-like hard scaly larger nodules on the extensor surfaces of the arms and hands. Some nodules appear on the soft palate.

¹⁹⁴Rothmann-St.: Xanthoma diabeticorum behandelt mit Quarzlicht. Zbl. 22: 7627, 1917.

The fresh lesions are transparent papules with central vesicles. Spontaneous involution occurs frequently. The spleen is large and hard. Serum cholesterol may be abnormal.²⁰¹⁸ The lesions contained five times the cholesterol of the



Fig. 273.—Lipoidosis cuti et mucosae (Urbach-Wiethe). (From Ramos e Silva, J. Arch. Dermat. & Syph., 1943.)

normal skin. Histological examination revealed an enormous extracellular lipid infiltration (mainly with cholesterol) and destruction of the elastic fibers. Even the apparently normal skin showed lipid infiltration of the vascular walls. Montgomery²⁰³⁷ after describing a similar case does not feel that the recognition of a new entity is justified. In contrast to Urbach's findings foam cells were present.

X-ray treatment was successful in a case of Frost and Anderson.²⁰³⁵

²⁰³⁵Frost, L., and Anderson, G. H. Extracellular Cholesterosis of Urbach. Arch. Dermat. & Syph. 106: 1039.

Lipoidosis Cutis et Mucosae (Lipid Proteinosis) (Urbach-Wiethe)²²⁴

This condition has been shown to be a definite clinical and especially histological and histochemical entity.^{227-247, 254} About thirty cases have been published showing a surprisingly uniform syndrome. The disease affects the skin and the mucosa in all the reported cases with nodular or hyperkeratotic lesions. Hoarseness in the first years of life is a characteristic early sign. A somewhat varioliform eruption appears during infancy and leaves irregularly outlined soft depressed scars. The hair growth is sparse. Later there is brown pigmentation and a scattering of yellowish very small papules on the face, the nape of the neck and the dorsa of the hands. The papules are not follicular.²⁴⁹



Fig. 74. Lipoidosis cutis et mucosae (Urbach-Wiethe). (From Ramos e Silva J. Arch. Dermat. & Syph. 1947.)

Irregular scarry ridges and patchy depressions give the face a characteristic knitted appearance at least in later years. Loss of the eyelashes, translucent nodules along the lids²⁴⁶ and indentations by scars add to the severe disfigurement. Especially in young persons some of the lesions bear crusts but there is no inflammatory border.²⁰⁵⁹ The corners of the mouth show vertical grooves.

²²⁴Urbach H. F. and Wiethe C. Lipoidosis cutis et mucosae (Virelows). Arch. path. Anat. 223: 245-319, 1929.

²²⁷Wiethe C. and Urbach H. Lipoidosis cutis et mucosae (Lipoid Proteinosis of Urbach). Arch. Dermat. & Syph. 31: 61, 1934.

²²⁸Quilzberger M. B. Case of Lipoidosis cutis et mucosae (Lipoid Proteinosis) (Urbach-Wiethe). Laryngoscope 52: 246-294, 1941.

²⁴⁹Ramos e Silva J. Lipoid Proteinosis (Urbach-Wiethe). Arch. Dermat. & Syph. 47: 301-3, 6, 1948.

²⁵⁰Campbell A. Lipoid proteinosis (Urbach-Wiethe). Br. J. Derm. 56: 669-675, 1944.

There are elevated firm elastic brownish yellowish white or flesh colored tumors on the extensor surfaces of the elbows and on the dorsal and lateral surfaces of the fingers. They are crowded together in warty mulberry like rough plaques.

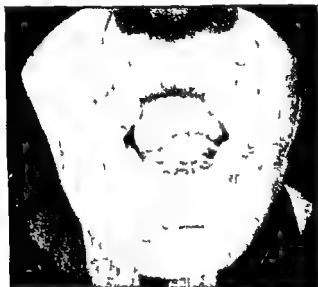


Fig. 75.—Lipoidosis cutis et mucosae (lipid protinosis) (Urbach Wiethe). Yellow nodules on the lips beneath the tongue and infiltration of lower lip. (From Wile U. J. and Snow J. G. Arch. Dermat. & Syph. 1941.)



Fig. 76.—Lipoidosis cutis et mucosae (lipid protinosis) (Urbach Wiethe). Numerous pea-like white papules along the margin of the lower lip. (From Wile U. J. and Snow J. G. Arch. Dermat. & Syph. 1941.)

In some cases the papules undergo early involution, persisting only on the elbows, the knees and the hands. The lips show on their inner surfaces fairly firm yellowish white plaques. Similar plaques and streaks occur on the palate in the pharynx and on the under surface of the tongue which is rigid and limited.

in its motion by a deep-seated infiltration and thickening of the frenulum. The papillae are mostly lost.¹⁰⁰¹ Similar thickenings symmetrically involve the tonsils and the larynx.

In the majority of the cases either glycosuria or latent diabetes is present. Heredity seems to play an important role. Consanguinity of the parents and familial occurrences are on record. Congenital hoarseness and developmental defects have also been observed.

Laryngotomy because of severe dyspnea from scarring has become necessary in several cases.

There can be no doubt that this is a characteristic syndrome. The outstanding histological features in both the skin and in the mucosa are (Wise and Rein¹⁰⁰²) an infiltration with a lipoid substance surrounding the vascular walls with massive deposits and vacuolization of the infiltrating masses seen in paraffin sections. Foam cells and double refraction indicating cholesterol esters are absent. The infiltration consists of a lipid probably bound to a protein.

Burger and Grut¹⁰⁰³ described a severe lipoidosis with extremely high lipemia, hepatosplenomegaly and a chronic eruption of small yellow elevated nodules on the extensor aspects and the buttocks. The lesions mainly contained phosphatides but no foam cells and no doubly refractile lipids.¹⁰⁰⁴

Gaucher's Disease is a slowly progressive often hereditary chronic lipidosis involving the spleen, the liver and the bone marrow. An uneven brownish tan pigmentation especially on the face is usually noticeable. Chloasma like often symmetric patches as well as streaky patterns have been seen.^{1005, 1006} Such symmetrical pigmentations may form quite characteristic leaden gray reticular cross patterns on the lower legs dotted with more intensely pigmented spots. In advanced cases the skin of the pigmented areas of the legs is glossy and scaly sometimes ulcerated. These pigmentations leave the soles, heels and toes free but they involve the instep areas in a sharply outlined spat-like fashion.¹⁰⁰⁷ There is a striking free margin just below the ankle. Leg ulcers without varicose veins occur. The mucous membranes may be pigmented but this is supposed to occur only if the adrenals are affected by the lipid deposits. The pigment is melanin. Brownish yellow triangular conjunctival thickenings occupying the interpalpebral space on both sides of the corner but leaving a thin white stripe around the corner appear slowly in the second decade. These pingueculae together with bone changes and splenomegaly establish the diagnosis.¹⁰⁰⁸ Purpuric tendencies occur at times.¹⁰⁰⁹ The specific lipid of Gaucher's disease which fills the large Gaucher cells in the involved organs is cerasin.

Niemann-Pick's Disease is another rare familial splenomegalic lipoidosis characterized by enormous accumulations of the dimunophosphatide sphingomyelin in the entire reticuloendothelial system. The disease is fatal within the

¹⁰⁰¹Bondoray L. Lipoid Proteinosis (Urbach-Wiethe) *Dermatologica* 33: 373-386 1941

¹⁰⁰²Bürger M. and Grütz O. Leber- und splenomegale Lipoidose mit xanthomatösen Veränderungen in Haut und Schleimhaut *Arch f. Dermat u. Syph* 180: 34-373 1932

¹⁰⁰³Bloom T. F., Groen J. and Postma C. Gaucher's Disease *Quart J Med* 5: 517-527 1936

first two years of life. The skin^{20, 9, 2064} of the infants is described as wrinkled, pale and profusely sweating. The subcutaneous fat disappears entirely. The exposed parts and also the mucous membranes are diffusely pigmented, and pigmented patches also occur in the mouth. The pigment is melanin and possibly due to adrenal involvement. ^{929 2064}

¹⁹⁶⁴Pick L. Niemann Pick's Disease and Other Forms of So-called Xanthomas. *Am J M Sc* 183: 601-616, 1933.

CHAPTER XXX

VII METABOLIC DISORDERS

Hemochromatosis

*Hemochromatosis*²⁹⁰³ *pigmentary cirrhosis in diabetes and bronzed diabetes* are terms mostly used to designate a disease characterized by the production of pigment in almost all organs diabetes in 78 per cent of the cases and hepatic cirrhosis. The disease occurs almost exclusively (95 per cent²⁹⁰⁴) in men mostly in the decade from 45 to 55 years. The disease was encountered five times among 100,000 hospital admission.²⁹⁰⁵ The onset is insidious with the symptoms of diabetes with abdominal pain or pigmentation of the skin.

The course depends on the diabetes and the cirrhosis. Before the advent of insulin about fifty per cent of the patients died in diabetic coma. Today the prognosis seems better since the outcome mainly depend on the course of the cirrhosis which may be protracted.²⁹⁰⁶ Primary cancer of the liver occurs in 7 per cent.²⁹⁰⁷

No specific treatment is known and though insulin may lengthen life the disease is ultimately fatal.

The striking pathological feature is the abundant production of pigment which is deposited in almost all organs though in varying amounts. The most heavily affected organs are the liver the pancreas the adrenal the salivary glands and the lymphatic nodes. There are two pigments present. *Hemosiderin* gives the iron reaction and *hemofuscin*²⁹⁰⁸ is an iron free melanin. The iron content of the organs which have been mentioned & the sites of the main deposits may be a hundred times higher than normal.

The etiology is not known. Familial occurrence has been observed.²⁹⁰⁹ Sheldon who has reviewed 345 cases in a comprehensive monograph classifies hemochromatosis as an *inborn error of metabolism* concerning the cells which later in life begin the cirrhosis of the liver and of the pancreas.

Dermadromes. The skin participates in the general process of *pigmentation* though not nearly as much as the liver and the pancreas. *Discoloration* is absent in only one sixth of the cases. The *melanoderma* develops insidiously and is the initial complaint²⁹¹⁰ in about one fourth of all instances.²⁹¹¹ It may precede the diabetic and hepatic symptoms by many years.²⁹¹² It is more

²⁹⁰³ von Recklinghausen E. Hemochromatose. *Versammlung Deutsche Naturforscher u Aerzte* Jellinek 1899. *Arch. f. klin. u. exp. Med.* p. 324. 1899.

²⁹⁰⁴ Sh. J. H. Hemochromatosis. London 1935. Oxford University Press.

²⁹⁰⁵ Cain J. C. Hemochromatosis. 6 Cases. *Texas State J. Med.* III 3 6-363 1910.

²⁹⁰⁶ Butt H. R. & J. W. L. W. M. Hemochromatosis. A Report of Thirty Cases Diagnosed During Life. *Proc. Staff Meet. Mayo Clin.* 22 6 67 1937.

²⁹⁰⁷ Lawrance R. B. Hemochromatosis and Heredity. *Lancet* 2 10 5 1935.

²⁹⁰⁸ Becker A. W. Shamberg D. Associated With Hemochromatosis. *Arch. Dermat. & Syph.* 24 340-342 1931.

often diffuse than patchy or freckled. In many instances the pigmentation covers the entire body but it is more pronounced in the parts exposed to the light and in the axillae the nipples the umbilicus and the genital region. As in Addison's disease scars may become heavily pigmented.

The color varies considerably.²⁰⁶⁶ In about twenty per cent of the cases the color is described as bronze ranging from a light bronzing to deep brown and even black. An equal group is characterized by the presence of a gray slate or bluish hue with a metallic reflection. The face tends to acquire a metallic sheen more readily than the body which usually remains brownish. The *metallic component* is more often seen in advanced cases. The oral *mucosa* particularly of the cheeks is often pigmented. The discoloration is more spotty than diffuse being brown or slate. The lips and conjunctivae may also become pigmented.

Except for the pigmentation the skin is not much changed. Dryness scaliness and pruritus may be troublesome.²⁰⁷¹ *Purpura* occurs in about fifteen per cent.²⁰⁷

Of great interest are the symptoms which indicate *endocrine* influences. They include atrophy of the testes and prostate impotence loss of axillary and pubic hair and thinning of the beard eyebrows and chest hair.²⁰⁷⁵

The pigmentation of the nipples and of the genitalia must be interpreted in the same way. Deficiency of urinary androgen and of adrenal cortical hormone has also been found. These endocrine features seem to be accompaniments of the hepatic cirrhosis which is such an important part of the syndrome (see hepatic cirrhosis).

The pigmentation increases with the progress of the disease. Improvement has only rarely been reported most often in connection with insulin treatment.²⁰⁸

As in the case in other organs the skin pigment is composed of hemosiderin and hemofuscin. The hemosiderin appears microscopically in fine granules most densely accumulated in the membranae propriae of the sweat glands and in the vascular endothelium while the hemofuscin appears in coarse deposits in the epidermis and in the corium. The ratio of the two pigments varies.²¹¹⁸ In some cases the hemofuscin is entirely absent (Roth after Krufmann¹¹³).

An iron reaction in the living skin has been devised by Fishback.²⁰⁷⁴ Intradermal injection of a mixture of equal parts of 0.5 per cent potassium ferrocyanide and one hundredth normal HCl produces a wheel which turns deep blue in the presence of iron after five minutes.

Diagnosis see Table I

Alkaptonuria and Ochronosis

A rare hereditary metabolic disorder in which the oxidation of the amino-acids tyrosin and phenylalanin is disturbed is called *alkaptonuria*. The urine

²⁰⁷¹Walther F. *Diabetes mellitus (Bronzediabetes)* Zbl. 39 131

²⁰⁷⁵Steinman H. P. and Ferris H. W. Hemochromatosis and Purpura. Arch. Int. Med. 59 23 239 1932

²⁰⁷⁷Labbe M. Bouillon R. and Lhuy P. Diabète sucré avec atrophie des organes génitaux et chute des poils (syndrome lésato-pancreato-génital). Bull. t. mém. Soc. méd. d. hôp. de Paris 80 15 4 1677 1934

²⁰⁷Fishback H. R. Clinical Demonstration of Iron in Skin. J. Lab. & Clin. Med. 25 91-92 1939

darkens on exposure to the air because of its content of homogentisic acid. This formation of pigment is closely related to the formation of melanin under normal and pathological conditions. After a long duration of alkaptonuria a dark iron free pigment, melanin like in character^{11,12} is deposited in the connective tissues, predominantly in the tendons and cartilages. Virchow called this condition *ochronosis*. The ochronotic tissues give a characteristic surface dis-



Fig. 24. Ochronosis. Left colored spot in ear. At right, articular dislocation. Note dark cartilages. (From Smith J. W., J. A. M. A.)



Fig. 25. Ochronosis. Slate colored spot indicating the insertion of the tendons of the muscular recti.

colorations wherever they are superficially enough situated. This is the case in the sclerotics, where slate colored or even black scleral spots appear on both sides of the cornea but separated from the limbus corneae by a narrow white strip. Thus 4 triangular figures with dark centers result. Obviously the site of these spots denotes the underlying insertion of the tendons of the rectus muscles. The influence of light may enhance the pigment formation.

Slit lamp microscopy reveals deposits of pigment in the *cornea*¹⁰⁷⁵ Other though less frequent and conspicuous gray greenish or even black discolorations are seen in the *ear* particularly the anthelix and concha the tip of the nose and in the upper eyelids Transillumination of the ears makes the cartilages visible as dark shadows⁶⁷⁶ The ear ducts and the nasal septum may also be discolored The cerumen may be black⁶⁷⁷ and homogénisic acid has been found in it

Diffuse pigmentation of the face sometimes to the degree of bronzing bluish discoloration of the knuckles the palmar eminences and the contact surfaces of the fingers have been observed^{1125 977 1078}

The *prognosis* depends on the development of destructive arthritis which occurs in the later stages

Chronic *phenol poisoning* from prolonged wet dressings with 1 — 3 per cent carbolic acid may produce the same changes as spontaneous ochronosis

The *morbidity* in fully developed cases is dominated by the black discoloration of the entire cartilage system

A low protein diet is advised in the management of ochronosis ■

Hyperuricemia—Gout

Purine substances are ingested mainly with liver and other viscera fish eggs and other foods rich in nucleoprotein A certain amount is synthesized in the body The end product of purine metabolism in the human organism is *uric acid* which is excreted in the urine mostly as urates

Gout is an unexplained disorder of the purine metabolism The values of the normal as well as the gouty uric acid level in the blood vary remarkably Figures over 2.5 mg per cent¹⁰⁷⁹ over 4.5 — 6 mg per cent^{112 1080 1081} and over 8.5 — 9.5 mg per cent are samples of what is considered *hyperuricemia* by various authors Deposits of urates in various tissues especially in and around joints^{1082 1083} are a characteristic feature Heredity seems to play a part¹⁰⁸⁴ Ninety five per cent of the gout patients are *males* About 5 to 8 per cent of the patients with joint disease have gout^{85 1085} It is still—as in Sydenham's time—¹⁰⁸⁶

¹⁰⁷⁹Smith J W Ochronosis of Skin and Corns Complicating Alkaptonuria Review of Literature and Reports of 4 Cases J A M A 120 13 1239 1947

¹⁰⁷⁸Swirsky M Y Ochronosis—Case With Alkaptonuria and Melanuria Clin 12 1373 1933

¹⁰⁷⁷Poulon V Ueber Ochronosis in Mensch und Tier in Beitr z path Anat u z allg Path 48 348 1910

¹⁰⁷⁶Pick L Ochronose Beriklin Wechnchr pp 478 509 5 6 531 1906

¹⁰⁷⁵Kinell J and Hagen R L Gout Review of 62 Cases M Clin No th Am rica 24 429-441

¹⁰⁷⁴Talbot J H Gout New York 1943 Oxford University Press

¹⁰⁷³McCracken J H 50 Cases of Gout Bull New England M Center 3 240 251 1941

¹⁰⁷²Hench P H Gout in U S A Proc Staff Meet Mayo Clin 12 6 69 1937

¹⁰⁷¹Hench P S Diagnosis and Treatment of Gout and Gouty Arthritis J A M A 116 453 1941

¹⁰⁷⁰Baur W and Klempere F Medical Progress in Gout New England J Med 221 691-695

¹⁰⁶⁹Hench P H The Diagnosis of Gout and Gouty Arthritis Proc Staff Meet Mayo Clin 11 476-480 1936

¹⁰⁶⁸Sydenham Th Th Work of Thomas Sydenham vol 2 London 1850 Syd uham Society pp 123 16

Fig 2 J



Fig 250

Fig 279 — Gout dormant tophus

Fig 250 — Gout

to some extent true that a higher social status (arthritis divitiarum of the old physicians) predisposes to gout.^{2887, 2888} Though manual work and poverty do by no means protect against the trouble. Most writers agree that overindulgence in certain foods as is common in the holiday season may precipitate an acute attack²⁸⁸⁹ in a gouty person.

The clinical picture of gout is dominated by repeated acute and extremely painful attacks of arthritis mostly in the small joints. Involvement of one big toe (podagra) is a frequent event. In spite of the acute inflammation there is no suppuration and complete restoration to normal function is the rule. The urinary excretion of urates is subnormal before and in the initial phase but increases rapidly during the attack.

In the chronic stage the attacks occur more frequently and last longer. More and also bigger joints become affected and urate deposits deform and destroy the articular cartilages. Tophi as the demonstrable deposits of urates are called often appear in the neighborhood of joints in and around tendons in the ears and occasionally in the subcutis.

Kidney function is often disturbed. The prognosis depends on the amount of articular damage, renal complications and the degree of cooperation by the patient in avoiding such foods which are prone to cause attacks. Colchicine relieves the acute attack and cinchophen improves the output of uric acid in the interval although many consider it too toxic. Salicylates are widely used as a less dangerous substitute. Hench⁶⁸ calls the therapy of gout which has not advanced since the advent of cinchophen a reflection on medical progress.

Dermadromes—The ruddy complexion and obesity¹⁰⁷⁸ of the typical gouty man are often mentioned. Sydenham spoke of his thick shaggy eyebrows and his full crown of hair.²⁸⁹⁰ The older literature emphasized and probably overrated the importance of gout in the etiology of dermatoses. Today to a large extent due to the skeptical attitude of J. Jadassohn (1905) who called the evidence scanty and uncertain the only recognized skin manifestation of gout is the tophus of the skin. The tophi are rarely present before or during the first attacks but they are almost invariably seen in chronic gouty arthritis.²⁸⁸⁶ Tophi in connection with the skin are seen in about one third of the cases about the small joints and on the ears. They are often found on the lateral aspects of the fingers but also about the elbows, knees and heels. On the ears where they occur in the vast majority of the cases of tophaceous gout^{2881, 2887} they most frequently occupy the helix. The tophi are nontender, very firm nodules of varying mobility. The size varies from a few millimeters to one centimeter in diameter but they are occasionally much larger. The color of the skin over superficial tophi is pale yellow. The nodules may ulcerate and in the contents microscopic needle shaped crystals of sodium urate may be found.^{1, 8, 2891}

²⁸⁸⁷ McCracken J. P., Owen Ph. C. and Pratt J. H. Gout Still a Forgotten Disease. J. A. M. A. 121: 367-372, 1946.

²⁸⁸⁸ Brachn r. Mortens n. K. 100 Gouty Patients. Acta med. Scandinav. 106: 81-107, 1941.

²⁸⁸⁹ Rutledge D. J. and Bedard H. E. Criticism for the Diagnosis of Presumptive (Pr. tophaceous) Gout. Management of an Illustrative Case. Proc. 41st Meet. Mayo Clin. 12: 149-156, 1937.

²⁸⁹⁰ Lichtwitz L. Gout. Bull. New York Acad. Med. 10: 306-319, 1934.

²⁸⁹¹ Christophers E. and Monroe S. E. Tophi of Feet. J. A. M. A. 110: 149, 1935.

The diagnostic value of typical tophi is great. Many clinicians have stressed looking at the ears in all cases of painful arthritis.

Pruritus is a frequent symptom of gout.¹² W. V. Goldsmith¹³ calls gout the most frequent cause of itching which certainly is not true in the USA. Pruriginous eruptions, urticaria and papular and bullous lesions have occasionally been seen paralleling the level of the hyperuricemia.¹⁴ Shavings of uric crystals were found in the lesions in some cases of papules and nodules of the skin of the lower legs.¹⁵ The same is true of psoriasis,¹⁶ erythromelalgia¹⁷ and especially of eczema. Kromayer¹⁸ the last to report a large series of gouty eczema saw its criteria in obscurity, recurrence in the same spot, location in unusual places not subject to external irritation, multiplicity of patches and the coexistence of various arthritic and neuritic complaints. Unfortunately his diagnosis and definition of gout are not up to the present standards but one should not dismiss lightly his impressions nor those of other experienced clinicians. Garrod (after Bulkley¹⁹) found that 47 per cent of 2000 patients with gout had eczema. Bulkley¹⁹ considered fully 30 per cent of his eczema patients as gouty.²⁰

Despite these impressive figures the relationship of gout and eczema remains controversial. It is now generally considered of small importance.

The blood uric acid in eczema—and for that matter also in pruritus, psoriasis and urticaria rises with a tendency to increased levels especially in severe cases.²¹ There is good reason to assume that in some of these cases the inflammatory and destructive processes in the skin are likely to be the cause of the hyperuricemia rather than its sequel.²² Injections of uric acid into the blood of patients with eczema have been shown not to influence the skin lesions.²³

Symmetric hyperkeratosis of the hands and soles together with erythema of the palmar eminences has been seen in several cases of hyperuricemia.²⁴ This condition occurs alone and also together with several internal disorders e.g. hepatic disease, the menopause and pregnancy so that no specific significance can be attached to the dermatosis. Many observations mostly older than twenty years are concerned with the role of hyperuricemia in psoriasis. Zorn²⁵ found that the scales in psoriasis contain a hundred times the amount of uric acid in the blood. He advises a purine free diet in eruptive psoriasis.

Thommasi and collaborators²⁶ have described an alopecia of the interolateral aspects of the lower legs about corresponding to the area supplied by the

¹²W. V. Goldsmith: *Erythema nodosum* and *erythema multiforme* 79, 1033, 1939.

¹³W. V. Goldsmith: *Erythema nodosum* and *erythema multiforme* 79, 1033, 1939.

¹⁴W. V. Goldsmith: *Erythema nodosum* and *erythema multiforme* 79, 1033, 1939.

¹⁵W. V. Goldsmith: *Erythema nodosum* and *erythema multiforme* 79, 1033, 1939.

¹⁶W. V. Goldsmith: *Erythema nodosum* and *erythema multiforme* 79, 1033, 1939.

¹⁷W. V. Goldsmith: *Erythema nodosum* and *erythema multiforme* 79, 1033, 1939.

¹⁸W. V. Goldsmith: *Erythema nodosum* and *erythema multiforme* 79, 1033, 1939.

¹⁹W. V. Goldsmith: *Erythema nodosum* and *erythema multiforme* 79, 1033, 1939.

²⁰W. V. Goldsmith: *Erythema nodosum* and *erythema multiforme* 79, 1033, 1939.

²¹W. V. Goldsmith: *Erythema nodosum* and *erythema multiforme* 79, 1033, 1939.

peroneal nerves together with slight atrophy of the skin and common baldness. These easily detectable hairless patches are supposedly suggestive of a high blood uric acid level.

Calcinosis of the Skin

It is difficult to characterize the internal disorder whose skin manifestations represent the various forms of cutaneous calcium deposits.



Fig. 281.—Calcinosis cutis. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

An exception is the metastatic calcinosis in which calcium deposits in the skin (striae) and other organs can be related to destructive bone disease, e.g. osteomyelitis¹¹⁰¹ or myelogenous leukemia (Wels after Sutton and Sutton¹¹⁰²).

The term *chalk gout* (Minkowski after Steinitz¹¹⁰³) is based on the similarity of nodular calcium deposits about small joints to the *tophi* of true gout. It is misleading in so far as an analogy to the uric acid metabolism in gout is not sufficiently apparent in the calcium metabolism in calcinosis.

¹¹⁰¹ Jadassohn J. Ueber kalkmetastasen in der Haut. Arch. f. Dermat. 200: 317, 1910.
¹¹⁰² Jadassohn J. Calcinosis circumscripta und Calcinosis universalis. Ergebn. d. inn. Med. u. Kinderh. 23: 216-275, 1931.

Cutaneous calcinosis occurs in two quite different types (Verse after Stein²¹⁰²) with relatively few transitional forms. In the so called chalk gout or *calcinosis circumscripta* the calcium deposits appear as circumscribed nodules mostly about the terminal phalanges of the fingers and on the extensor aspects of the elbows. The volar surface of the finger tips is often the first location.²¹⁰³ The legs are rarely affected except for the patellar area. The size of the nodules ranges from mustard seed to pea or even walnut size. Multiple deposits may simulate shots in the X ray picture. The nodules are usually nontender. Acute painful inflammations of the par-articular tissues resembling gout may occur but they leave the joints and bones free.²¹⁰⁴

Superficial nodules may ulcerate and extrude calcareous material. The mouth of such sinuses is often surrounded by a hard yellow ring.²¹⁰⁵ The nodules may become fused globular tumors¹⁹⁴ or the covering skin may be depressed and atrophic.



Fig. 28. Localized calcinosis circumscripta sinus formation. (Courtesy Dr. G. Cooper.)

On the whole, chalk gout in itself is not a severe disorder. The nodules may disappear spontaneously.^{108, 2106} Life is rarely in danger. However, 40 per cent of the cases²¹⁰⁷ are combined with scleroderma, Raynaud's disease and acrodermatitis atrophicans.

²¹⁰²Epstein I. Idiopathic Calcinosis Cutis. Arch. Dermat. & Syph. 31: 367-377, 1936.

²¹⁰³Maloney E. R. and Bloom D. Cutaneous Calciosis. Arch. Dermat. & Syph. 33: 245, 1931.

²¹⁰⁴Swanson W. W., Forster W. G. and Hol A. Calcinosis Circumscripta. Am. J. Dis. Child.

45: 500-503, 1935.

²¹⁰⁵Wheeler F. P. Improvement in Cases of Calcinosis Uniusualis in Children. Brit. J. Dermat.

47: 400-404, 1935.

²¹⁰⁷Atkinson E. R. D. and Wheeler F. P. Cutaneous and Subcutaneous Calciosis. Brit. J. Dermat.

48: 207-310, 1935.

The female patients with chalk gout outnumber the males about 3 to 1. The disease occurs most often in persons beyond the thirty fifth year of life and the onset has repeatedly been seen connected with the menopause.^{2108, 2110} It appears rarely in the young^{2105, 2111} at lactation or at puberty.²¹¹² Familial occurrence is known.²¹¹³

In the diffuse variety of calcinosis known as *calcinosis universalis* any part of the skin may become affected though there is a tendency to involve the neighborhood of the big joints. Symmetry is a feature and a decrease in the number of deposits towards the acra is often apparent.



Fig. 43.—Male aged 83 years. Large subcutaneous calcareous plaque existing for many years. Secondary infection and sinus formation.

The lesions develop in crops with fever and general reactions. The course is progressive so that finally almost the entire skin may become involved. Large calcareous plaques in or under the skin may form and ulcerate. Deeper structures may become affected and a septic syndrome with fever, immobility of muscles, multiple chalk abscesses and cachexia may result. The evacuation of large chalk abscesses may improve the picture. In some cases several quarts of chalky matter could be drained from huge cold abscesses.¹⁰ In chronic

- ¹ Astruc H. Hergert and Hessman B. H. Ein Fall von Kalkgicht. *Hygies* 91: 646-694, 1932.
 Zbl. 43: 477.
²¹ I. ntoppia B. Subcuta. Kalkknoten bei pluriglandulärer Insuffizienz. *Hospitalistid* 111.
 1. 19: 1. 711: 1. 41.
² Cuhrau H. Beitrag zur Frage der Kalkansammlung in der Haut. *Dermat. Wchnsch.*
 80: 117-116, 19.
¹¹ Jacobowitz H. Ein besonderer Verlauf form bei Calcinosis universalis. *Zurich. J. kind. ch.*
 53: 507-601, 193.
¹² Ce lands I. Ueber Kalkgicht. Fall. Diss. 1931. Marburg a. d. L.
¹³ Welt. b. b. R. J. Francon F. and Robert P. Calcinosis universalis et arthritide che.
 Paris med. 1932 II: 43.

is a peculiar form of *systemic amyloidosis* which not only produces an unusual dermatosis, but follows a different pattern in the distribution of the amyloid avoiding the spleen and the large glands which in the typical cases contain the largest deposits of amyloid. Instead the smooth and the striated muscles



Fig 284



Fig 285

Fig 284—Localized amyloidosis (Courtesy Division of Dermatology Department of Medicine University of Chicago)

Fig 285—Amyloidosis cutis (lichen amyloideus) (Courtesy Dr H E Littredge)

including the heart are the site of widespread amyloidosis.^{2124, 2125, 2126} Enlargement, fissuring and nodularity of the tongue was present in all cases. There may be difficulty in closing the mouth and the gait may be shuffling. The clinical aspect of the skin in some of the cases^{2127, 2128, 2129} is characterized by transparent or yellow waxy small high firm papules which cover some areas very densely.

²¹²⁴Lubarsch O. Zur Kenntnis ungewöhnlicher Amyloidablagerungen. Virchows Arch f path Anat 271: 867-890 1922.

²¹²⁵Königst in H. Amyloid der Haut. Haut u Geschl 4: 3: 254-357 1932.

²¹²⁶O'Leary J A, Montgomery H and Brunting M A. Systematized Amyloidosis of the Skin and Mucous Membranes. Rence-Jones Prot Internat Arch Dermat & Syph 21: 408-409 1935.

²¹²⁷Bosellini G L. Sopra i amidi mucocutanea. Česká Dermat pp 57-62 1931. Zbl 44: 470.

²¹²⁸Mollow W. Zur Klinik der systematisierten Amyloidose. Verhandl d deutsch Gesellsch f Inn Med pp 555-559 1930.

The eyelids, scarp, the pubic and adjoining areas the palms the dorsa of the feet and other sites have been seen covered with the lesions which at first glance because of their transparency give the impression of vesicles. Atrophy telangiectases and purpuric spots are other features. In some cases the lesions were very firm large nodules^{131 132} or large sclerodermatic plaques.¹³⁴

All the patients were middle aged or older.¹³⁴ Multiple myelomas and Bence Jones proteinuria have been found in some cases.^{21 4}

The presence of amyloid in the living skin can be demonstrated by the subcutaneous injection of 0.1 per cent solution of congo red in saline. The produced red spot fades within 4 days in normal skin but remains visible up to 12 days if amyloid is present at the site of injection.^{133 136}

The amyloid forms a band in the upper cutis the epidermis being atrophic and free of amyloid. The vascular walls and the muscles contain large deposits. The spleen and the large glands have no amyloid or only along the blood vessels.

¹³¹ Gottron H. *Arteriosklerose und Hämorrhagien in der Haut*. *Arch. f. Anat. u. Z. f. exp. Med.* 1913. *Ergebn. d. Anat. u. Z. f. exp. Med.* 23: 2.

¹³² Gottron H. *Chromatose und andere Färbungsstörungen der Haut*. *Arch. f. Anat. u. Z. f. exp. Med.* 1913. *Ergebn. d. Anat. u. Z. f. exp. Med.* 23: 2.

¹³³ Mairas A. *Amyloidose der Haut*. *Arch. f. Anat. u. Z. f. exp. Med.* 1936-1937.

¹³⁴ Gottron H. *Myelomatöse Hautveränderungen*. *Arch. f. Anat. u. Z. f. exp. Med.* 1936-1937.

¹³⁵ Marchionni A. and John J. *Die Amyloidose der Haut*. *Arch. f. Anat. u. Z. f. exp. Med.* 1936-1937.

¹³⁶ Hilgert G. and Freshman A. W. *Amyloidose der Haut*. *Arch. f. Anat. u. Z. f. exp. Med.* 1936-1937.

CHAPTER XXXI

METABOLIC DISORDERS

Vitamin Deficiencies

Avitaminosis A—Vitamin A is a fat soluble heat resisting unsaturated alcohol which is easily destroyed by oxidation. It is formed in the liver from its precursors the yellow or red carotenes which occur in widely differing amounts in fruits vegetables and animal fats. The daily vitamin A requirement of the human organism is 3000 5000 I U.

Deficiency of vitamin A causes night blindness because the visual purple and the visual violet develop from Vitamin A. Xerosis conjunctivae is another early ocular symptom occurring together with the cutaneous epithelial changes. A specific protective function of vitamin A against infections which was assumed earlier^{217 218 140} is now doubted^{1778 141}.

The most often used test for vitamin A deficiency is the measuring of the dark adaptation of the eyes. This is done by determining the threshold amount of light which must be used to illuminate a given surface in order to render it visible. The readings after light and dark adaptation are then compared^{214 215}. The value of the dark adaptation test for vitamin A deficiency has recently been questioned¹⁴⁴. The determination of the concentration of vitamin A in the blood plasma will probably be a better indicator of deficiency than the dark adaptation¹⁷⁷⁹ but so far only little work with spectrophotometric determinations of the vitamin A content in connection with skin changes has been done²¹⁴.

The fat droplets containing vitamin A are highly fluorescent in ultraviolet light but lose this property rapidly in ultraviolet light¹⁴⁶. Surprisingly enough

²¹⁷Schärf F. Leben die Bedeutung der Vitamine in der Dermatologie. Zbl. 66 6 7-591 1933 1934.

²¹⁸Pratt M. H. Vitaminis in Dermatology. N. Clin. North America 26 47-64 1942.

¹⁴⁰Pratt M. H. and Scharlau B. Der Einfluss gesteigerte Vitaminzufuhr auf experimentelle Staphylokokkeninfektion der Haut. Ztschr. f. d. ges. exp. Med. 71 465-476 1930. Zbl. 35 8 2.

¹⁴¹Pratt M. H. Wette. Versuche über die Einwirkung von Vitaminen und Calcium auf experimentelle Staphylokokkeninfektionen der Haut. Ztschr. f. d. ges. exp. Med. 77 418 2 5 1931. Zbl. 39 990.

¹⁴⁴Sternberg Th. and Pillsbury D. M. Influence of Avitaminosis A on Experimentally Produced Cutaneous Infections in Rat. Arch. Dermat. & Syph. 35 247 2 1931.

¹⁷⁷⁸Brunsting L. A. A. 19th and C. Dark Adaptation in Itchy Skin. Arch. Dermat. & Syph. 43 4 461 1943.

¹⁴⁶Carleton A. and Steven D. Keratosis Follicularis. Arch. Dermat. & Syph. 48 143 1 0 1943.

¹⁴⁷Walters J. H. Dark Adaptation in Skin Conditions. Ohio Stat. M. J. 40 5 4 528 1944.

¹⁴⁸Ruch H. M. Brunsting L. A. and Osterberg A. E. U. of Vitamin A Tolerance Test in Certain Cases of Dermatological Disorders. Proc. Staff Meet. Mayo Clinic 21 909-17 1946.

¹⁴⁹von Querenfeld. Mikroskopisch Nachweis von Vitamin in animalen Gewebe. Klin. Wchnschr. 16 1213 1 17 1935.

in examinations with the fluorescence microscope vitamin A has been found to be absent from the epidermis even after the feeding of high doses²¹¹⁷

It is likely that vitamin A is concerned with the lipids. Experimental hyper-vitaminosis A results in accumulation of cholesterol in the adrenals, the skin and other organs²¹¹⁸ so that lesions develop which are comparable to those of Schuller-Christians disease. Circumscribed alopecia is also a feature of this experimental disease.



Fig. 94. Infant 16 months of age. Follicular hyperkeratosis in vitamin A deficiency with xerophthalmia. (From Frazier et al., Hu et al. and Chu et al. Arch Dermat & Syph 1943)

Dermadromes—Hyperkeratinization is an effect of vitamin A deficiency on the epithelium, has been known for a long time (Morris after Schuller²¹¹⁹). In the rat it leads to the appearance of keratinized cells in the vaginal mucosa, a phenomenon resembling estrus.

In the human skin the effects of vitamin A deficiency are also dominated by hyperkeratinization²¹²⁰. Dryness caused by impaired function of the keratinized oil and sweat glands is the first symptom. Frazier and Hu²¹²¹ and inde-

²¹¹⁷Cornbleet Th. and Popper H. Properties of Human Skin Revealed by Fluorescence Microscopy. The Normal Skin. The Vitamin A Content of the Skin Arch Dermat & Syph 40: 59-65 1942

²¹¹⁸Collaro J. A. and Rodriguez J. C. Hypervitaminosis A durch Fütterung von reichem Vitamin an junge Ratten. Klin Wochenschr 11: 173-1734 1933

²¹¹⁹Mashkoffelson L. N., Byamovitch F. B., Krichinskaya H. H. and Shatamova L. V. Vitamins in Pathogenesis and Treatment of Skin Diseases. Am Rev Soviet Med 3: 19-27 1945

²¹²⁰Frazier E. V. and Hu C. K. Cutaneous Lesions Associated With Deficiency in Vitamin A. In Man Arch Int Med 40: 507-514 1931

pently Loewenthal²¹¹ described a characteristic dermatosis which occurred frequently in persons who had lived on a diet deficient in vitamin A and who suffered from night blindness, keratomalacia and/or xerophthalmia. The eruption which was called *phrynoderma* or toad skin by Nicholls²¹² healed after treatment with vitamin A or an adequate diet.

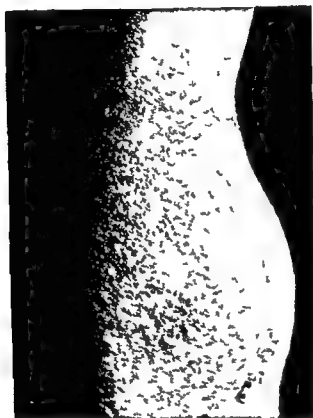


Fig 287 — Male aged 13 years. Diffuse follicular hyperkeratoses (*phrynoderma*) in vitamin A deficiency (From Fraser C N, Hu C H, and Chu F T. Arch Dermat & Syph 1943.)

Phrynoderma consists of disseminated somewhat grouped *perifollicular papules* with a central keratotic plug or spine. In severe cases²¹³ the papules are large, flat or hemispherical, sometimes acneiform without suppuration, sometimes more like lichen planus. Slate-colored hyperpigmentation may occur in and around the lesions. The eruption is usually abundant and symmetrical, predominantly appearing first on the anterolateral aspect of the thighs and the

²¹¹ Loewenthal L J A. A New Cutaneous Manifestation of the Syndrome of Vitamin A Deficiency. Arch Dermat & Syph 28: 700-05 1933.

²¹² Nicholls L. *Phrynoderma*, A Condition Due to Vitamin Deficiency. Indian Med Gaz 63: 641-656 1933.

²¹³ Faal P. Clinical Manifestations of Vitamin Deficiency in the Malay States. Arch Dermat & Syph 60: 160-166 1944.

posterolateral aspect of the upper part of the fore arms spreading from here to the extensor surfaces of the arms and legs the shoulders abdomen chest back and buttocks.²¹³ Itching is a frequent complaint. There is absence of visible sweating so that the articular folds become dry and scaly. Diffuse branny scaling itching is also often noticeable especially in Negroes.²¹⁴ The colored skin is apt to lose its natural sheen.²¹⁵ The lack of oiliness helps to differentiate this papular eruption from acne.

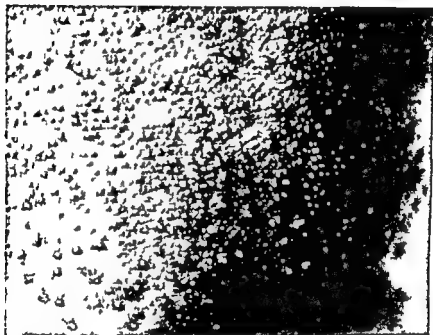


Fig. 2. Male aged 14 years. Projecting spin. h. f. follicular hyperkeratosis in vitamin A deficiency (From Frazier C. N., Hu C. K. and Chu P. T. Arch. Dermat. & Syph. 1913.)

Comedones are common not only in adolescents but also in older persons. Brittleness and grooving of the nail²¹⁶⁻²¹⁸ is a feature of vitaminosis A. Loss of luster of the hair caused by dryness and alopecia are frequently observed phenomena.^{214, 217}

Phrynodermia usually precedes the ophthalmic symptoms²¹⁴ which sometimes are completely absent. Pillat²¹⁹ describes a characteristic pigmentation of the

²¹³Lehman E. and Rapaport H. B.: Cutaneous Manifestations of Vitamin A Deficiency in Children. J. A. M. A. 114: 386-393, 1940.

²¹⁴Reis, F.: Contribution to Cutaneous Manifestations of Vitamin A Deficiency. Chinese M. J. 50: 945-949, 1936. Zh. 55: 295.

²¹⁵Gill, A.: Alopecia Circumscripta Due to Vitamin A Deficiency. Case. Arch. Dermat. & Syph. 51: 110-111, 1945.

²¹⁷Ellat, A.: Ernährungsgesetze. Edited by W. Stepp. Berlin, 1939. Julius Springer.

²¹⁸Frazier C. N. and Hu C. K.: Nature and Distribution According to Age of Cutaneous Manifestation of Vitamin A Deficiency (207 Cases). Arch. Dermat. & Syph. 32: 5-552, 1936.

²¹⁹Ellat, A.: Über die eigenartige pigmentartige der Bluthaut bei den verschiedenen Formen der Vitamin A-Mangelkrankung der Fische. Graef. s. Arch. 127: 575-597, 1931.

conjunctivae most marked in the caruncula plica semilunaris and the lower fornix. The pigmentation may outlast the deficiency state after treatment with vitamin A.



Fig. 930.—1. Illula hypoleuca in vitamin A deficiency with xerophthalmia. (From Fraile, C. N., Hu, C. I., and Chu, P. T., Arch. Dermat. & Syph. 1943.)

The *histopathologic* features are epithelial hyperplasia and hyperkeratinization with associated follicular keratinization and degeneration of the hairs as well as of the sweat and oil glands.^{158, 160} There is some inflammation in the corium but no pustulation. The disease is not rare among children¹⁶¹ as had been originally assumed. The closer the age groups are to puberty the more likely they are to be affected.¹⁶¹ This is in line with the well known tendency to follicular keratosis in acne juvenilis.

Among children with verosis of the skin without phrynodermia the sexes are equally affected. In adult groups the patients are almost exclusively males.¹⁶² Strumfjord¹⁶² has tried to explain the formation of verruca caseosa by the absence of the antikeratinizing vitamin A in later fetal life. A small group of pregnant

¹⁵⁸Moult, F. H., Histopathology of Rat Skin in Avitaminosis A. Arch. Dermat. & Syph. 47: 768-7, 1943.

¹⁵⁹Fraile, C. N., Hu, C. I., and Chu, P. T., Variations in Cutaneous Manifestations of Vitamin A Deficiency From Infancy to Puberty. Arch. Dermat. & Syph. 48: 114, 1943.

¹⁶⁰Strumfjord, J. V., Verrucae Caseosa: A Manifestation of Vitamin A Deficiency. Acta Derm. 48: 341-3, 1940.

women who were treated with high daily doses of vitamin A during the last six months of pregnancy had babies with less vernix than usual.

The response of phrynodermia and the other dermatoses to dietary treatment and vitamin A in daily doses of 100 000 to 300 000 I U is usually prompt within two to four months. The sebaceous secretion was often restored within two weeks. The recognition of a follicular keratosis as a specific manifestation of vitamin A deficiency by Irazier and Wu stimulated investigation of the nature of other follicular keratoses. Pick²¹⁴ found in eight out of ten cases of Darier's disease the blood vitamin A below normal and in nine cases he was able to improve the hyperkeratotic symptoms of this hereditary disease which up to then had been largely considered incurable. The vitamin A level in the blood rose under treatment with approximately 200 000 units daily.

Pick^{214 215} believes Darier's disease to be a congenital disorder of the absorption of the vitamin A or of the conversion of carotene by the liver into the final product. Pick's work has been confirmed in several instances^{216 217} of this rare dermatosis but resistant cases have also been found.²¹⁸

The follicular keratosis in *psoriasis rubra pilaris* (Devergie's disease) prompted Brunsting²¹⁹ and Sheild to analogous investigations. In three cases the threshold levels of dark adaptation were much higher than normal. Under vitamin A treatment the night blindness and later also the cutaneous changes improved materially. The vitamin A content of the blood has several times been found low.^{219 220} The good results of treatment with vitamin A have been confirmed in some cases.^{219 220}

Treatment with vitamin A has been found beneficial in various forms of excessive or abnormal keratinization particularly in dermatoses which have the features of dryness (xerosis) and follicular or other hyperkeratosis such as acne vulgaris, calluses, corns,^{221 222 223} pruritus, keratosis vulvae,²²⁴ lichen pilaris,²¹⁴ keratotic lichenoid plaques of the legs, ichthyoform erythroderma in Hodgkin's Disease with hepatic involvement,²¹⁶ scaliness of the external auditory canal,²²⁵ nummular eczema,²²¹ brittleness of the nail,²²⁶ dryness of the skin in diabetes²²⁷ and keratosis blennorrhagica.²²⁸ It has been recommended in ointments for the treatment of burns and slow healing wounds and ulcers.²¹² The

²¹⁴Pick H M, Chargin L and Gosholtz H. Keratosis Follicularis (Darier's Disease) A Vitamin A Deficiency Disease. Arch Dermat & Syph 42: 177, 1941.

²¹⁵Pick H M. Keratosis Follicularis (Darier's Disease) Treated With Vitamin A. Arch Dermat & Syph 45: 633, 1942.

²¹⁶Cornfield T, Tupper H, Williams F. Blood Vitamin A and Cutaneous Diseases. Arch Dermat & Syph 48: 103, 1944.

²¹⁷Wein A L and Levine A A. Ichthyoid Rupture of Familial Type. Arch Dermat & Syph 48: 285, 1943.

²¹⁸Straumfjord J V. Vitamin A. Effect on Acne. Northwest Med 42: 1025, 1943.

²¹⁹Obermayer M F and Frost K. Some Effects of Vitamin Therapy in Dermatology. Arch Dermat & Syph 51: 309, 1945.

²²⁰Glazebrook A J and Tomaszewski W. Ichthyiform Atrophy of the Skin in Hodgkin Disease. Vitamin A Metabolism. Arch Dermat & Syph 50: 85, 1944.

²²¹Johnson J H. Vitamin Therapy. Laryngoscope 52: 80, 1942.

²²²Groes P. Nummular Eczema. Arch Dermat & Syph 46: 1060, 1941.

²²³Draser J G and Cutler A C. Vitamin A Deficiency in Diabetes. Arch Int Med 55: 22, 1940.

²²⁴Löh W. Die Behandlung großer flacher Verbrennungen mit Ibertran. Chirurg 6: 263, 1934.

cod liver oil containing salves are an example. Vitamin A in high doses has been found ineffective in ichthyosis.²¹⁷⁴

All the mentioned indications cannot yet be considered established.²¹⁴⁴ The therapeutic doses of vitamin A range from 50 000 to 200 000 units daily. In spite of the fact that the blood serum level of vitamin A has been frequently



Fig. 290 —Pityria is rubra pilaris (Courtesy Dr. M. Jequier)

found to be low in widespread dermatitis, eczema and psoriasis, no curative effect of vitamin A therapy could be observed in such cases.²¹⁷⁵ The level of vitamin A in the blood plasma of 50 patients with diverse dermatoses was essentially normal.²¹⁶

²¹⁷⁴Peck J. M., CHEA W. and CHAGI L. Vitamin A Study in Cases of Ichthyosis. Arch. Dermat. & Syph. 48: 17-32, 1943.

²¹⁷⁵Marchioni L. A. and FATH G. Vitamin A—und Carottingehalt des menschlichen Bluteserums bei Hautkrankheiten. Arch. f. Dermat. u. Syph. 175: 419-437, 1937.

²¹⁷⁶Cornbleet Th., FIPPER H. and GILMANN I. Blood Vitamin A and Cutaneous Diseases. Arch. Dermat. & Syph. 48: 103-106, 1944.

Carotenemia Xanthosis—*Carotinemia auranthiasis* (Bickel after Kaufmann¹¹⁷) or *xanthosis* (Von Noorden and Salomon)¹¹⁸ after Salomon¹¹⁷ (manifests itself by a yellow discoloration of the serum and of large areas of the skin. The yellow color which may have varying ochre or sulfur shades suggests at first glance icterus but the sclerae are white and the mucous membranes are usually of normal color with the exception of the palate. Another distinguishing feature is the distribution of the yellow pigmentation. The nasolabial folds, the axillae and the palms and soles are the sites of the most intense discoloration in slight cases the only sites. In contrast to icterus pruritus is absent unless caused by diabetes. There are no complaints other than the disfigurement.

The urine is light compared with an icteric urine although carotene is excreted in the urine.

The history and physical examination almost regularly reveal that the patient had lived for a long time on a vegetarian diet that he is a diabetic or both.

The yellow substance which causes the discoloration has long been identified as carotene. The carotenes are red orange or yellow oxygen free hydrocarbon with 40 C atoms which by hydrolysis form the alcohol vitamin A. All green leaves (not the yellow leaves in fall) carrots pumpkins yellow squash oranges especially some Japanese varieties and many other fruits contain carotenes. Animals are unable to form carotene but they take it in and store it in the liver the fat the retina the corpus luteum and the adrenals. It causes the yellow color of the butterfat the body fat and of the egg yolk. Carotene does not appear in the sweat.¹¹⁹ The horny layer of the epidermis has a marked affinity for carotene which explains the normal yellow hue of the palms soles and calluses.¹¹⁹

Carotinemia has often been seen in babies fed with carrots. It was frequently observed during the First World War in Germany.¹¹⁷ where at times most of the population was compelled to live almost exclusively on rutabagas carrots and other vegetables. It is also prevalent in the Japanese island where the fish and meat supply is scanty. After feeding infants with carrots for a very long time the carotinemia may disappear in spite of continuing with the diet. The system apparently adjusts itself and becomes able to step up the splitting of carotene. The alimentary carotinemia particularly in infants is harmless and disappears quickly after a change in the diet (Diabetic carotinemia see chapter on Diabetes).

Vitamin D (viosterol and activated 7 dehydrocholesterol) is stored mainly in the liver but also in the skin and in other organs. One of the known functions of vitamin D is the maintenance of the absorption of calcium and phosphorus from the intestinal tract.¹²⁰ The most important vitamin D deficiency disease is rickets.

No dermatosis caused by vitamin D deficiency has been established. Therapeutic success with daily doses of 50 000 to 400 000 units have been reported in

¹¹⁷Salomon H. Psoriasisformen nach Mohr rube guss Münch h n med Wchnschr 66 564 1919

¹¹⁸Kauffmann and Drigal kl Carotin Vitamin A f m hlich n Organismus Klin Wchnschr 300 309 1933

¹¹⁹Edward E A and D ntl y 9 Q Pigment and Color of Living Human Skin Am J Anat 1-33 1939

pemphigus^{150 151} but confirmation has remained lacking²¹³. The treatment has also been given a trial in psoriasis^{18 2183} and acne vulgaris. Though 80 per cent satisfactory results were claimed in a large series¹⁸⁴ the method has not found general recognition¹⁸⁵.

Vitamin E comprises a group of more than 130 substances^{17 6}. Experimental avitaminosis E manifests itself by sterility, muscular dystrophy, paralysis and other symptoms according to the animal used. Many seed germ oils, particularly that of wheat, contain vitamin E which has so far not become of recognized dermatological importance. Its successful use in acrodynia has been reported¹⁸⁶.

Vitamin K (menadione) occurs most abundantly in green leaves e.g. spinach, alfalfa and cabbage. It is also synthesized by several bacteria e.g. *Escherichia coli*. Its absence inhibits the *prothrombin* formation in the liver. When the prothrombin drops to about 10 per cent of normal in chicks kept on a vitamin K free diet the bleeding tendency appears²¹⁸⁷. In man obstructive jaundice through the absence of bile salts in the intestines impairs the absorption of adequate amounts of vitamin K and thus creates hypoprothrombinemia with a subsequent hemorrhagic tendency (Brown and Bancroft 1935 after Quick¹⁸⁰). Therefore the picture of avitaminosis K is that of hemorrhagic disease which may cause purpuric skin manifestations. In the adult it results most often from severe disease of the liver from short circuiting operations or chronic diseases of the intestinal tract. For the role of vitamin K in the hemorrhagic disease of the newborn see chapter on newborn page 394.

The Vitamin B Complex—According to Elvehjem²¹⁸⁸ the B complex consists of at least a dozen separate factors which vary widely in their chemical structure and physiological effects. Deficiency in any one of the B vitamins is usually complicated by a deficiency in another B vitamin or by a deficiency in some other vitamin^{189 190}.

¹⁵¹ Buttsworth T. Pemphigus Improvement Following Vitamin D. Arch. Dermat. & Syph. 41: 670, 1940.

¹⁵⁰ Ting H. and Hamilton C. M. Pemphigus Controlled by Vitamin E. Arch. Dermat. & Syph. 41: 517, 1939.

¹⁸⁴ Wright C. A. Vitamin D Therapy in Dermatology. Arch. Dermat. & Syph. 42: 145-154, 1940.

¹⁸⁵ Lilj y H. C. Psoriasis Arthropathia Treated With Vitamin D. Arch. Dermat. & Syph. 41: 931, 1940.

¹⁸⁶ Maynard. Vitamin Therapy in Dermatology Especially Vitamin E for Acne. Arch. Dermat. & Syph. 41: 842-857, 1940.

¹⁸⁷ Impson C. E. E. F. A. and H. I. by Smith H. Vitamin D in the Treatment of Acne. Arch. Dermat. & Syph. 41: 835-837, 1940.

¹⁸⁸ Foran O. H. K. D. as Treated With Vitamin K at Cern. M. J. Australia 1: 78, 1941. Abstr. Arch. Dermat. & Syph. 45: 3.

¹⁸⁹ Quilley A. J. The Coagulation Defect in Sweet Clover Disease and the Hemorrhagic Chick. J. Biol. Chem. 129: 201, 1940. A Correlation of the Nature of Prothrombin. Am. J. Physiol. 128: 260, 1940.

¹⁹⁰ Elvehjem C. A. Water Soluble Vitamins. Handbook of Nutrition. Chicago 1943. American Medical Association.

¹⁹¹ Jolliffe N. Recent Advances in Clinical Applications of the B Vitamins. J. Am. Dietet. A. 17: 10-11, 1941.

²¹³ Plow T. H. B. and W. B. A. and W. F. A. Note on the Role of Vitamin B in Human Nutrition. J. A. M. A. 122: 414-415, 1939.

A vitamin B deficiency should be suspected in indigent groups in persons with peculiar food habits (e.g. alcohol addicts in persons who live mainly on sweets and in dietary faddists) and in patients with diseases altering the vitamin B requirement.²¹¹² Jolliffe²¹¹³ mentions in this connection prolonged abnormal strain, manic depressive psychoses, fever of long duration, hyperthyroidism, pregnancy, lactation, rapid growth, diarrhea of long duration, polyuria, gastrointestinal fistulae, and liver and stomach diseases.

Thiamine—The richest sources of thiamine are yeast, pork, oatmeal, peanuts and other seed, and liver. Spinach, tomatoes, oranges, apples, and white unfortified bread are poor in this vitamin. Without the use of whole grain cereals or enriched bread, it is difficult to meet the adult daily requirement of 1.5 to 2.1 mg.²¹¹⁴ Symptoms of thiamine deficiency²¹¹⁵ include anorexia, fatigue, insomnia, nausea, constipation, headache, precordial distress, and a group of more tangible neurological manifestations like symmetric polyneuritis, especially of the legs, followed by central symptoms known as Wernicke's syndrome. Finally, there occurs a group of circulatory disturbances including edema, serous effusions, and circulatory collapse. These circulatory manifestations occur in about one third of the patient with polyneuropathy. All the mentioned symptoms, together with their many variations, form the *beriberi* complex.



Fig. 291. Cheilitis and perleche in riboflavin deficiency. (Courtesy Dr. O. H. Pitt-Jones and The Lippincott Company.)

The only well established early, and therefore important, skin manifestation in *beriberi* is the burning of the soles of the feet and numbness of the dorsum and lower part of the ankle.^{2116, 2117} Glossitis, perleche²¹¹⁸ and other skin manifestations probably belong to associated vitaminoses.²¹¹⁹ The expected pain relieving

²¹¹²Sharples, L. H. Burning feet in labourer on sugar plantation in British Guyana. *J. Trop. Med.* 32: 355-360, 1929.

²¹¹³Straus, M. H. Article in the Vitamin. Chicago, 1939. American Medical Association.

²¹¹⁴Kagawa, S. Ueber Riboflavinmangel am Mundwinkel. *Der H. A. Haminoke Mitt. d. med. Gesellsch. zu Tokio* 46: 115-116, 193. *Zbl.* 63: 66.

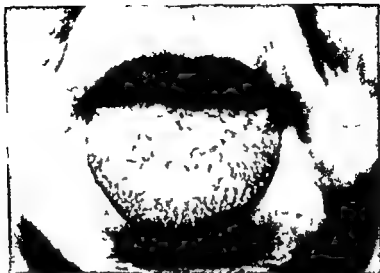


Fig. 20 —Loss of papillae stiffens and increases redness of the tongue in vitamin B deficiency (Courtesy Therapeutic Notes Parke Davis & Company)

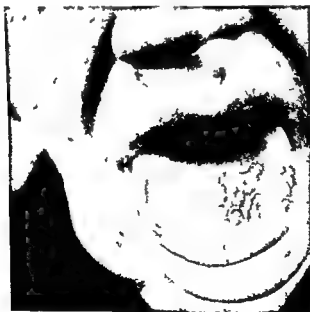


Fig. 23 —Vitamin B deficiency —Loss of papillae stiffens resulting in slick floured tongue (Courtesy Wisconsin Central Hospital)

and curative effect of thiamin in herpes zoster and postherpetic neuralgia has failed to materialize.¹¹⁹

Riboflavin—This vitamin is a yellow crystalline heat stable but light labile¹²⁰ substance. It functions as an enzyme in tissue respiration. Liver, milk and vegetables are the best sources. The daily minimal requirement can be met with one serving of liver or one quart of milk. Experimental riboflavinosis can be retarded growth, dermatitis and catarrh in rats, paralysis from myelin degeneration in chicks and dogs, and opacities in the cornea of various animals.

Dermatomes—In man, vascularizing keratitis is usually the first to appear. It may be followed by glossitis and dermatomes. Sebrell and Butler¹²¹ gave eighteen adult women the so-called Goldberger Finner diet¹²² which does not contain meat, milk or yeast, but consists mainly of lard, cornmeal, casein,



Fig. 94. Vitamin B deficiency. Inset. Tongue is inflamed, is sore, flat, pigilla bluish, mouth started to bleed. It appears. (Courtesy Dr. Carroll Cooper.)

tomato juice, cod liver oil and other items low in riboflavin and nicotinic acid. Within three to four months, ten out of the eighteen persons developed pallor of the lips at the angles of the mouth without involvement of the buccal mucosa. This pallor was soon followed by maceration, bilateral superficial transverse fissures extending downward from the angle in some instances as much as one half of an inch. Thus, typical perleche developed. There was little inflammatory reaction. The lesion remained moist and became covered with a yellow crust. The lips became eroded and red along the line of closure. Sebrell and Butler¹²³ called this labial affection *cheilosis*. In addition to the cheilosis there was a fine seborrheic desquamation on a slight erythema in the nasolabial fold on the alae nasi, in the vestibule of the nose and on the ears.

¹¹⁹Battner H. and Roll H. C. Herpes Zoster and Vitamin B. J. A. M. A. 122: 2585-56, 1939.

¹²¹Sebrell W. H. and Butler R. F. Riboflavin Deficiency in Man. Int. Health Rep. 32: 25-2281, 1934.

¹²²Goldberger J. and Tanner W. F. The Action of Dried Bacteria on Dried Milk and Brewed Yeast. Pub. Health Rep. 40: 5180-192.

Other authors^{2189 2197} observed *filiform excrescences of a seborrheic nature* in the nasolabial folds and their surroundings resembling urea frost in conditions which they felt to be due to riboflavin deficiency *

The experimental cheilosis healed promptly on crystalline synthetic riboflavin while nicotinic acid failed to cure it. Spontaneous cases of cheilosis are not infrequently found among alcoholics and other persons liable to become vitamin B deficient. Jolliffe²¹⁹⁷ et al demonstrated that many of these spontaneous cases of cheilosis responded to synthetic riboflavin but not to thiamin, nicotinic acid or pyridoxin (also see Finnerud¹⁹⁸)

In some cases of ariboflavinosis the tongue has been found purplish red fissured and with enlarged papillae¹⁹⁹. Riboflavin in doses of 2.5 to 50 mg given by mouth heals cheilosis from riboflavin deficiency sometimes strikingly in a few days¹¹⁰ but of course fails to do so when the perlèche or cheilitis are due to other causes¹⁹⁸ e.g. ill fitting dentures or sensitivity to light. Cheilosis is also a common feature of pellagra in children.⁹⁰

Sydenstricker⁹¹ and others have described *ocular symptoms* especially an early vascularizing keratitis accompanied by inflammation of the limbic plexus and conjunctiva bulbi in the interpalpebral space. Photophobia is a characteristic complaint. The slit lamp is necessary for early diagnosis. The keratitis resembles the form often associated with rosacea but it is bilateral, responds to riboflavin and shows a different vascular pattern.

The validity of the syndrome cheilosis, keratitis and glossitis as a manifestation of ariboflavinosis has recently been doubted because of the failure of riboflavin to cure it in 20 cases²⁰⁰. Riboflavin has lately been recommended in the treatment of eczema.^{203 204}

Rats with chronic hyporiboflavinosis showed in contrast to other avitaminoses a heavy infestation with lice which disappeared after feeding them riboflavin.²⁰⁵

Nicotinic Acid (Niacin) Pellagra—Nicotinic acid (niacin) and nicotinamide (niacin amide) are the components of two pairs of heat stable (Chick and Roscoe²⁰⁶) coenzymes concerned with respiration and carbohydrate metabolism¹⁸⁸. A deficiency disease in dogs called blacktongue has since the work of Goldberger and his coworkers in the early twenties been con-

These pseudo-seborrheic changes should not be confused with seborrheic dermatitis which is accompanied by oily hair and skin.

²¹⁹⁷Jolliffe N, Fein H B and Rosenblum L A. Riboflavin Deficiency in Man. New England J Med 221 921-9 6 1939

¹⁹⁹Flann and C W P. The Nosologic Status. JAMA 128 737-740 1944

¹⁹⁸Jolliffe N. The Preventive and Therapeutic Use of Vitamins. JAMA 129 613-617 1945

²⁰⁰Jioui H C. Riboflavin Deficiency Among Chinese. Cheilosis and Seborrheic Dermatitis. Chinese M J 52 314 1941. Abstr Arch Dermat Syph 46 561

¹⁹⁰Sydenstricker E V, P S Brell W H, Cleckley H M and Kruse H D. Ocular Manifestations of Ariboflavinosis. JAMA 114 2437-44 1940

²⁰³Macchella T B E and McDonald P R. B Vitamin in the Human Subject. VI. Failure of Riboflavin Therapy in Patients With the Accepted Picture of Riboflavin Deficiency. Am J Med Sc 205 214-23 1913

²⁰⁴Landon J V. Deficiency of Vitamin B₂. Lancet 1 1365 1370 1939

²⁰⁵Kristensen K F and Vedlitz N. Treatment of Eczema With Vitamin B Complex. Lancet 1 170 1940

²⁰⁶Gyorgy P. Pediculosis in Rats Kept on a Riboflavin-deficient Diet. Proc Soc Exp Biol & Med 28 343 1934

¹⁰Chick R and Roscoe M H. Heat-Stability of Vitamin B₂. Biochem J 24 105-11 1930

sidered analogous to human pellagra. In 1937 Ikehjem discovered that nicotinic acid would cure canine blacktongue. Deficiency of nicotinic acid is generally believed to be the main cause of pellagra though clinical pellagra is considered now to be a multiple vitamin deficiency^{207, 208} which is often associated with symptoms of beriberi²⁰⁹ riboflavinosis²¹⁰ (Hou after Ottenstein²) sprue²¹¹ and scurvy.

Liver and yeast are the richest natural sources of nicotinic acid. Corn contains only about one fifth of the nicotin content of wheat and the refined flours of both grains lose almost the entire amount. Nevertheless even refined wheat flour still contains three times as much nicotin as refined corn flour. The peculiar scarcity of nicotin in corn accounts for the frequency of pellagra in countries where the diet of the poor consists predominantly of corn flour products. The first medical writer on pellagra the Spaniard Casal in 1762 already suspected the use of corn flour in the poor peasant population as one of the causes of pellagra¹¹. We know now that other deficient diets may cause pellagra too. Alcoholism and chronic gastro intestinal disease are the most important causes of pellagra in countries without endemic pellagra¹². Among 102 cases in Baltimore about one third were due to alcoholism one third due to malnutrition and one third secondary to other diseases^{13, 14}. Chronic gastric ulcer cancer of the stomach and surgical removal of large parts of the stomach or bowel are conditions which predispose to pellagra¹⁵.

The main centers of endemic pellagra are found in some warm mediterranean countries and in the southern U.S.A. The tropics as well as the cooler climates have only sporadic cases mostly alcoholics insane or patients with gastric disorders. The incidence has become smaller in the main centers e.g. Italy²¹¹ (Lavinder after Scie Harn²¹²) where the morbidity of 104 067 in 1881 had diminished to 55 029 in 1905 probably due to improved living and eating conditions. At the same time the mortality was reduced to about one tenth. Thus in the last decades pellagra has become a rare disease in the classical pellagra country. A decided trend to the better also prevails in the southern U.S.A. where the incidence has been reduced by more than 50 per cent from 1929 to 1936²¹³. Today pellagra is no longer a major public health problem.

¹¹⁰⁷Gordon F R and 4 ver ghan T L Vitami Therapy in General Practice Chicago 1940
Th Year Book Publ h m Inc

¹⁷⁰⁴Flv h j m ■ A ■ itation of Nicotini A l d to f ellagra. *Physiol* ■ v 20 949 1940

¹⁹Uji i ra f i i lagra Ned ri tijaehr v g nevk pp 949 950 1933 Zbl 46 167

1. Synthesis of NAD⁺ in cell L. F. Templeton G. M. at I. Weaver J. W. Riboflavin Deficiency Human Subject J. A. M. 112 1637 1700 1939

¹² [1] H. S. Chinnail, *Eng. Sci. Lond.* 1911, The C. & M. Co.

31. Eland, J. J., and Winkler, N. B. Lethargy Among Chronic Alcoholic Addicts. *JAMA*

99 764-371 1029

¹¹¹ Bogg T H and Patrick I I *Flaga 10° Cases Bull Johns Hopkins Hosp* 50 21-32 193

2215 Wheeler G A and S F H W H Control of Pellagra J A M A ■ 95 09 1932

²² Spies T H and de W H F. Observations on the Etiological Relationship of Severe Alcoholism to Pellagra. *Am J Hyg* 196 5 155 1933

²²¹⁷Eusterman G B and O'Leary P A. Pellagra Secondary to Benign and Carcinomatous Lesions and Dysfunction of the Gastrointestinal Tract. Thirteen Cases. Arch Int Med 67, 633-641

Lesions and Dysfunction of the Gastrointestinal Tract Thirteen Cases Arch Int Med 47 633-649 1921

in the Union though it is far from being stamped out. In 1938 3 205 deaths from pellagra occurred mostly in the southeastern states. It is remarkable that the southwest has a very low pellagra rate.

The ages between 20 and 45 years seem to be most susceptible (Lavinder after J. Jadassohn¹¹⁹) but no age group is immune. Many large statistics show a dominance of the female sex. Menstruation pregnancy and lactation are provoking factors. The distribution of the lesions suggests strongly that sunlight is an important pathogenetic element yet a great number of observations of typical lesions in covered skin (vulva) and of lesions restricted to the typical areas in children who did not wear any clothes prove that exposure to light is not the only provoking factor¹²⁰ though one of great importance in the eruptive stage¹²¹ or after a prolonged deficient diet¹²¹. Some authors even claim a beneficial influence of sunlight in pellagra in some stages¹²² (for extensive discussion of the sunlight factor see also Seale Harris¹²³).

Lack of a gastric intrinsic anti pellagral factor¹²⁴ and failure of the liver to store and utilize nicotinic acid are much discussed pathogenetic factors¹²¹.

The word *pellagra* is derived from the Italian *pelle agra* sharp burning skin or from the Latin *pellis aegra*—sick unhealthy skin. The skin manifestations however though characteristic do not represent the most serious part of the syndrome.

Usually the disease¹²⁵ starts in the spring of the year, with increasing lassitude and muscular weakness especially of the legs which make the patients slow moving and resort to the use of canes a suggestive symptom well known to physicians in pellagra regions.

Already in this early stage burning of the seemingly still normal skin particularly of the feet a burning sensation in the throat which cannot be soothed by cold water and other paresthesias cause discomfort. The patients avoid the heat and lie uncovered in bed. Headache and sudden attacks of dizziness or falling without coma convulsions or nystagmus are typical nervous symptoms. The reflexes are increased the pupils are small¹²⁶. Psychoses of widely varying seriousness develop frequently. The facial expression of the patient is often a worried fearful melancholic or stuporous one¹²⁷. Such patients cry easily and are depressed sometimes in realization of the deterioration of their faculties. In severe cases hallucinations depression even mania delirium suicidal at

¹¹⁹Merck L. and Jadassohn J. Die Pellagra. Handb. d. H. u. Gk. 4 2 377-537 1933.

¹²⁰Fliake R. Die Lokalisation der pellagrösen Hautveränderungen und rauen Schweiß mit Wechnach. 150-153 1934.

¹²¹Smith D. T. and Rumm J. M. Effect of Sunlight on the Clinical Manifestations of Pellagra. Arch. Int. Med. 55 631-645 1937.

¹²²Spies T. D. Pellagra II. Dermatitis and Sunlight. Arch. Int. Med. 56 970-976 1935.

¹²³Sydenhater V. P. Armstrong E. S. D. Erick C. J. and Kemp P. G. On the Existence of an Intrinsic Deficiency in Pellagra. Am. J. M. Sc. 192 19 1936.

¹²⁴Kleinmann H. Beiträge zur Frage der Pellagra. Arch. d. H. u. Gk. 11 1859-1894 1930 271 28 743.

¹²⁵Rum J. H. Die Hautveränderung der Pellagra. Dermat. Ztschr. 55 30-312 1900 also Zbl. 24 133 136.

tempts and other manifestations of psychosis develop.^{228, 229} On the other hand psychosis with a long confinement to institutions is a predisposing factor to pellagra.²³⁰

The internal symptoms are dominated by various phases of inflammation of the *gastrointestinal tract*. These disturbances most often account for a fatal outcome.²³⁰ The oral symptoms will be described later.

Anorexia is an early symptom. Nausea, vomiting and diarrhea are common though greatly varying in intensity. Free HCl is absent in more than 66 per cent^{231, 232} and the pepsin content is low. The stool, no matter of what consistency, are nearly always foul.²³³ Anemia is present in about 50 per cent.^{232, 234} Diabetes insipidus has been observed frequently. Urinary porphyrin has been found according to the extent and acuity of the skin manifestations. It is a coproporphyrin which has but a weak light sensitizing effect. Porphyrin excretion was



Fig. 15. Pellagra. Extensive dermatitis on right hand follows gastric acid (alcohol) exposure to a light beam. (Clinical Pellagra, The C. V. Mosby Co.)

²²⁸Stotopolky H. Zum Vorkommen i pellagroider krankungen bei Alkoholikern und Gistee krankern. *Schw. med. Wchnst.* 62: 297-301 1932.

²²⁹Chotze M. Klinisch Beitrag zu Kenntnis der psychischen Zustände des Neurologischen und Psychiatrischen. *Arch. Psychiat. u. Neurol.* 148: 170-210 1933.

²³⁰Cecchi J. and Byer A. Zur Klinik und Genese der Pellagra. *Monatsschr. Psychiat. u. Neurol.* 78: 296-355 1930.

²³¹Frank G. Ueber Pellagra in Irrmanst. *Monatsschr. Psychiat. u. Neurol.* 78: 461-465 1933.

²³²Goetz M. and Mayer C. Beitrag zum Studium der Magenaffektion bei Pellagra. Der Einfluss des Histamins auf die Achylie. *Monatsschr. Psychiat. u. Neurol.* 78: 377 1930. *Zbl. B.* 537.

²³³Guthrie J. B. Achylia in Pellagra. *J. Trop. Med.* 35: 71-74 1933.

²³⁴Flinker R. Das Blutbild bei Pellagra. *Folia haemat.* 49: 149-155 1933. *Zbl. B.* 45: 439.

²³⁵Turner H. Pellagra. *Arch. Dermat. & Syph.* 25: 960-96 1932.

²³⁶Rassulev J. A. Diabetes insipidus bei Pellagra. *Arch. f. S. hiff. u. Tropen Hyg.* 88: 481-489

found negative in the interval between the attacks.²⁵ Urinary porphyrin has occasionally been found in alcoholics with or without pellagra.²²⁶ Fever is generally absent but in some cases a spiking fever with diarrhea may create a typhoid resembling rapidly fatal disease.^{227, 228}

Dermadromes—Skin manifestations of pellagra appear in the majority of the cases.²²⁹ They do not cause such dangerous complications as the gastro intestinal and neurological symptoms but they are of great diagnostic even path



Fig. 296.—Early pellagra. Dermatitis over the feet. (Courtesy Dr. Henry F. Hall, Jr. and the Upjohn Company.)

ognomonic importance. Together with the sometimes dubious internal complaints they give the syndrome of pellagra its character as a well defined entity.

²²⁵Heckh W., Ellinger E. and Spies T. D.: Porphyrins in Pellagra. *Quart. J. Med.* 8: 305-319, 1937.

²²⁶Kark H. and Mikhelson A. P.: Pellagra and Porphyrinuria. *Am. J. M. Sc.* 201: 340-395, 1941.

²²⁷Ginsburg D.: Sporadic Cases of Pellagra in Northern Russia. *Soviet Med. J.* 575-58, 1931. *Zh.* 41: 64.

²²⁸Margaret J. and Rimbaud I.: Typhose pellagreuse. *Bull. Soc. Franç. de dermat. et syph.* 38: 1361-1364, 1931.

The outbreak of typical *pellagra erythema* occurs suddenly sometimes preceded by a premonitory deciduous macular eruption²¹⁹ on the dorsa of the hands. The true erythema of pellagra appears most frequently at first on the dorsa of the hands. In contrast to *eczema* this lesion is solid and well defined. Even in sunlight exposed and tanned forearms the pellagra erythema rarely extends higher up than the wrist line. The palms remain free. The pellagra erythema frequently stops at the knuckles but it may invade the extensor surfaces of the fingers.²²⁰



Fig. 97—Pellagra erythema of Casal. (Courtesy Dr. M. J. Har.)

Occasionally the erythema affects the flexor aspects in a strap or cuff like bridge; if this occurs it is considered an important diagnostic sign²²¹. The instep is the site of an additional erythema. Here the inflammation extends from a line right above the ankles to the base of the toes. In analogy to the hands the dorsa of the toes are only occasionally involved. The erythema may also appear on the face. The bridge of the nose is most frequently erythematous but diffuse or confluent always symmetric patches may occupy the whole face. In the confluent type polycyclic patterns may appear. Facial erythema is more often encountered in women and children than in men and it is often inconspicuous²²². Narrow bands of skin along the hair line and around



FIG 208.—Pellagra. Collar of Casal. Ch Ritis. (From Harri Seal. Clinical Pellagra.)

the mouth remain normal. This mask-like distribution is similar to that of chloasma.

The fourth typical site of pellagral erythema is a ring of varying width around the entire neck. This is called the necklace or collar of Casal. In the typical instances, Casal's necklace extends into the sternal area as a berloque shaped appendix.

The elbows, knees (Bass after Seale Harris²³³), shoulders, scrotum, perineum, vulva and infra-mammary areas^{233, 234} are some of the less common sites. Sym-

²³³Contello M. J. Pellagra in Unusual Locations. Arch. Dermat. & Syph. 46: 7-14, 1942.

²³⁴Jordan T. J., Ellis H. and Rubinowitz A. M. Unusual Sites of Lesions in Pellagra. Arch. Dermat. & Syph. 46: 661-664, 1942.

metry is a pronounced sometimes astonishing feature¹⁰. The skin on which the erythema develops is often slightly edematous. At first the erythema consists of confluent pink blotches but within a week it takes on a bright scarlet red color which later has a copper or mahogany hue¹¹.

A few days after the appearance of the erythema the epidermis *cracks and fissures* develop. In some cases vesicles, blisters, pustules and other forms of secondary infection may appear with a predilection for the hair follicles of the dorsa of the fingers. These follicles are often blackened with non removable



Fig. 93 - Vulvul of pellagra. (From Harris: *Syphilis*, Clinical Pellagra.)

dirt. In the early part of the second week the erythema reaches its peak. A pink halo up to 2 cm in width may surround the lesions. A few days later the acute symptoms recede and ichthyosiform keratosis, peeling, deep fissuring and increasing pigmentation become the dominating features. The pattern of ridges and furrows is coarsened. *Follicular keratoses* appear in the erythematous areas. On the hands they may be inconspicuous but on the bridge, the tip and the sides of the nose and in the *nasolabial folds* they may form grater like patterns.

This follicular hyperkeratosis about the nose has been referred to as *seborea*^{12, 13}. The facial follicular hyperkeratosis is a frequent and characteristic clinical feature of pellagra¹⁴.

The centers of the pellagral areas begin to clear up during the fourth week. The horny layer comes off in large flakes, sometimes in sheets of the size of the entire lesion. A scaly hyperkeratotic margin may remain for some time.

The typical attack of pellagral erythema is over in 6 to 10 weeks. Pellagra usually occurs in *repeated attacks* mostly in spring and early summer although recurrences in fall occur occasionally. In winter time the patient is usually free of symptoms. The repeated attacks of erythema on the dorsa of the hands leave the skin in an increasingly *atrophic* condition which of course is not reversible.



Fig. 300. Neglected pellagra. Thick red flured and pigmented lesions extending far beyond the commonly involved dorsa of the hands. (From H. H. H. *Clinical Pellagra*.)

Longitudinal yellowish stripes (sometimes referred to as *striae*) are caused by underlying extensor tendons which can be seen through the thin atrophic skin in moderately strong dry light^{211 212} *Oral manifestations* occur in about one half of the cases (Sandwith after J. J. Idelson²¹³). They are important because some of them, e.g., burning and salivation, are among the earliest symptoms. The descriptions of the tongue in pellagra vary. Swelling and coating are early

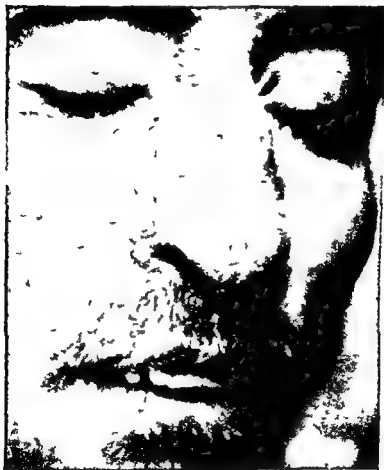


Fig. 301. So-called *leaden tongue* of the nose in pellagra. (From Harris & al., *Clinical Pellagra*.)

symptoms. Denudation may occur on the margins and on the tip while the dorsum remains coated^{2219 2220}.

In fully developed cases the fungiform papillae may be reddened and swollen (raspberry tongue) or in later stages atrophic, thus giving the appearance of a slick, bald, thin tongue. Fissures and ulcerations, black hairy tongue, brown coating, ulceration and other lesions have been observed. In acute stages the entire oral mucosa may be fiery red. Aphthous lesions are common²²¹⁸.

The *lips* may show small red erosions and there may be angular fissures. Plaut-Vincent's infection of the gums is a common finding in pellagral stomatitis.⁴¹

Vaginitis and vulvitis with much discharge and occasionally edema of the clitoris and labia minora is often called an important or even pathognomonic symptom.



Fig. 30.—Pellagra. Typical dermatitis of the feet and of the patellar region. (From Harris: *Sexual Chlamydia*.)

The *nails* are usually not affected. The *hair* is often shed during the attacks and complete alopecia has been seen to develop. The loss of the lateral part of the eyebrows is frequent and may have some endocrinological significance (see

⁴¹ Kassirsky, J., and Burrows, L.: Zur Klinik der Pellagra in Mitteleuropa. Arch. f. Schiffs- u. Tropen Hyg. 36: 323-336, 1932.

chapter on Endocrines) Of interest is the observation of koilonychia and achylia gastrica (Plummer Vinson syndrome) in a woman with pellagra¹¹¹

Epithelioma of the skin is a surprisingly rare complication in pellagra dermatitis¹¹²

The occurrence of repeated seasonal attacks has already been mentioned Many variations in course and symptomatology have become known so that the diagnosis in nonendemic cases may be extremely difficult or even impossible in the absence of skin manifestations The term *pellagra sine pellagra* is used for such cases Internal symptoms usually precede the erythema for a considerable time¹¹³ According to Merck the erythema rarely remains absent longer than one year after the first symptoms Slight erythema may well pass unnoticed It is probably for this reason that the incidence of dermatomes has in some large series only been 45 per cent¹¹⁴ There is no relationship between the degree of the erythema and the severity of the internal symptoms



Fig. 103. Typical dermatitis of the dorsal aspect of the hands. Erosions and crusts from Harris' case. (Clinical Illustrations)

Of great interest are the variations of the clinical picture in various countries and in the same country at different times Thus Casal's necklace and the involvement of the instep areas is relatively common in southern Europe especially the Balkans and rare in the U. S. A.

¹¹¹ Follow W Nagelverdrung in bei Pellagra Arch f Schiffs u Tropen Hyg 41 391-393 1937

¹¹² Rutledge W U and Kelly R Epithelioma secondary to pellagra dermatitis Arch Dermat & Syph 23 107 1975 1931

¹¹³ Efremow V Etiology Pathogenesis and Prophylaxis of Pellagra VI para 160 para 16 bole 2 261 276 1933

The post mortem *pathology* is unrevealing. The most striking feature is the severe hepatic atrophy or fatty degeneration. As can be expected the skin shows keratosis, parakeratosis, pigmentation and atrophy according to the stage. There is degeneration of the elastic fibers and perivascular infiltration and hyaline degeneration of the vascular walls.^{2, 45} The unaffected skin also shows hyperkeratosis, atrophy and inflammation though in a lesser degree.⁴⁶

The diagnosis is a clinical one since satisfactory laboratory methods have not yet been worked out. One has to consider eczema in which there are no mucosal symptoms and no atrophy and erythema exudativum multiforme in which the primary lesion is a coin shaped erythematous urticaria often with a central vesicle. Acrodermatitis atrophicans takes a slow nonseasonal course and has its typical localization and pityriasis rubra pilaris is nonseasonal and there is no pronounced involvement of the typical pellagra sites although niacin is reportedly effective.¹⁷ The diagnosis of pellagra is easy in endemic and fully

FIG. 104. Atroph tongue in piliagra (from Harri¹ al. Chit¹ i piliagra).

developed cases but difficult in sporadic and incomplete cases. The typical sites, the sharply outlined lesions, the seasonal attacks, atrophy, nutritional peculiarities including chronic gastrointestinal disease and alcoholism and the combination of internal and skin manifestations will often assure the diagnosis if its possibility once enters the physician's mind. Incomplete syndromes²⁴ may cause great difficulties in the differentiation from pernicious anemia,²⁵⁻²⁸ sprue, Addison's disease and other entities.

Arzt u. Mat. d. n. zur Erforschung d. r. Jellagra. Diss. H. Ku. 1933. Zbl. 45. 457

D rmat & Syrh 46 100-111 1941

7 1910

⁴⁶Wheelwright, A. A. Note on the History of Malaria in the United States. *Pub. Health Rep.* 2: 20, 1925.

Proc. of the R. Soc. Med. 32: 3-370 1934

196-006 (1971 77) 48 6

As a diagnostic sign one has to add successful treatment with nicotinic acid²²¹ and a balanced diet. More than one thousand successfully treated cases (nicotinic acid) were reported in 1941 when Seale Harris published his monograph on pellagra. Oral treatment with nicotinic acid in divided doses totaling 500 mg daily supplemented by vitamin B complex and vitamins A, C, D and E is recommended (Spies et al. after Gordon and Scrimgeour²²²). After a week 100 mg per day is sufficient. Ruffin and Smith²²³ advise injections of about 100 mg daily. Injections and larger doses by mouth are followed by flushing of the face together with a feeling of heat and tingling²²⁴. This harmless side-effect can be avoided if the nicotinic acid is given with the meals or replaced by nicotinic acid amide²²⁵.

A high caloric diet with the emphasis on meat, liver, eggs, milk and fresh vegetables, removal from slum housing and reduced exposure to sunlight are other important therapeutic factors. Stomach preparations (ventriculin) have been recommended by several authors²²⁶⁻²²⁸. This medication is based on the discovery of an intrinsic pellagra preventing factor in the gastric juice²²⁹.

The prognosis is now better and recovery is often dramatic unless irreversible damage to the nervous and gastrointestinal systems or severe cachexia has developed. In spite of liver diet or medication the mortality in large American series was still 20 to 31²³⁰ and even 50 per cent²³¹ 10 years ago but almost zero in private practice²³². With the use of nicotinic acid and other vitamins the mortality has probably been lowered. Many authors stress the importance of prolonged treatment after clinical cure.

The pellagra preventing effect of nicotinic acid has been proved²³³.

Pyridoxine has been used with encouraging results in the treatment of adolescent acne. The doses varied from 50 to 250 mg daily in divided doses²³⁴. Seborrhea and an acroderma resembling syndrome have been seen in pyridoxine deficient rats²³⁵⁻²³⁶.

²²¹Ruffin J. M. and Smith D. T. Treatment of Pellagra With special Reference to the Use of Nicotinic Acid. South M J 33 40-4 1933

²²²Gollamith C. A. and Corliss W. The Vaso Dilating Effects of Nicotinic Acid. Am J M Sc 208 204 209 1943

²²³Eckhardt J. Pellagra-probi in Med Klin 33 159 161 1937

²²⁴Petri C. and Waische O. Treatment of Pellagra and Polyneuritis With Stomach Preparations. Hospitalid 79 1003 1004 1936 Zbl 66 309

²²⁵Petri C. Waische O. Stubbe T. Glibjaerg E. and Stubbe Tegilaerg H. P. Treatment of Pellagra With Stomach Preparations and the Gastroenteric Etiology of Pellagra etc. Acta med Scand 135 450-460 1937 Zbl 111 350

²²⁶Gullit T. Glibjaerg H. I. Neurological Problems in Pellagra. Treatment With Ventriculin. Hospitalid 80 841 844 1937

²²⁷Smith J. H. Pellagra. Resume Internat CH 2 120-134 1933

²²⁸Gjlenstrick R. V. I. and Armstrong F. S. 440 Cases of Pellagra. Arch Int Med 59 883 891 1937

²²⁹Spies T. M. Grant J. M. Stone R. F. and McLester J. B. Recent Observations on 600 Pellagras. Nicotinic Acid in Prophylaxis. South M J 33 1231 1237 1939

²³⁰Jolliffe N. Rosenbaum L. A. and Sawhill J. The Effects of Pyridoxine (Vitamin B₆) on Peristaltic Activity. Arch Derm 5 143 149 1952

²³¹Eckhardt J. C. Gylberg L. and Johnson L. V. Influence of Factor in Blood Which Enhances Bacterial Growth Activity in Relation to Riboflavin. Proc Soc Exp Biol & Med 46 40-409 1941

²³²Sullivan M. and Nicholls J. Nutritional Approach to Experimental Dermatology. Nutritional Dermatoses in the Rat. II. Vitamin B₆ Deficiency. J Invest Dermat 3 300-345 1940

According to Gordon and Sevrinhaus²⁰⁷ pyridoxine is able to heal cheilosis quicker than riboflavin²⁰⁸. Some pellagra cases may heal only after addition of pyridoxine to the other vitamins²¹⁰. The healing effect in seborrheic eczema atopic dermatitis and eczema²⁰⁴ still lacks confirmation.

No cutaneous manifestations in man have definitely been related to deficiencies of *panthothemic acid*, *choline* and *biotin*. Panthothemic acid prevents the greying of the hair in rats fed on a B complex free diet.²¹¹ A substance in uncooked eggwhite called *avidin*²⁰⁸ is able to inactivate the vitamin *biotin* (vitamin H). Dermatitis of the feet in the chick and alopecia in rats fed on a diet containing much raw egg white have been observed and some data pointing to analogous phenomena in man are available.^{212,213} The so called egg white injury in the rat has been cured by the addition of excess biotin²¹³ to the eggwhite rich diet or by inactivating the avidin by cooking. A *para amino benzoic acid* deficient diet causes graying of the fur of rats which can be cured by feeding this substance.²¹⁴ There is some evidence that repigmentation of gray hair in man may be stimulated by oral administration of *para amino benzoic acid* or calcium panthothenate. The changes produced in some persons were only of theoretical value since in the majority of the cases with any change at all an unsightly yellow or greenish cast was produced sometimes together with scattered wiry black hairs.^{215,217} No satisfactory restoration of the hair color which could compete with dyeing has been accomplished.²¹ Some results of prolonged oral medication with *para amino benzoic acid* in vitiligo have been reported.²¹⁸

Inositol is required to maintain the fur of the mouse.²²⁴ Stryker and Halbeisen²²⁵ observed that 32 out of 42 cases of unexplained and noncharacteristic dermatitis about the neck and face were accompanied by moderate macrocytic anemia. These cases responded at once to proper diet and liver extract which in the opinion of the authors was due to the vitamin B complex.

Avitaminosis C—Scurvy—*Vitamin C* or *ascorbic acid* occurs in many animal and plant tissues especially in the adrenal cortex from which it was first

²⁰⁴ Macchia, Th. E. Studies of the B Vitamin in the Human Subject. *Am. J. Med. Sc.* 203: 114, 1942.

²⁰⁵ Wright, C. S., Samitz, M. H. and Brown, H. Pyridoxin in Dermatology. *Arch. Dermat. & Syph.* 47: 6: 1-6, 3, 1943.

²⁰⁶ Linn, K., Richard, G. V. and Sampson, W. L. Studies on Nutrit. Achromot. Ichth. in Rats. *J. Nutrition* 22: 553-563, 1941.

²⁰⁷ Gyorgy, P., Rose, C. G., Eakin, R. E., Snell, E. E. and Williams, H. J. Egg White Injury. *Non Absorption of Biotin. Scien.* 62: 477-48, 1941.

²⁰⁸ Sydenstricker, V. I., King, S. A., Briggs, A. F., De Vaughan, V. M. and Ish, H. H. Egg White Injury in Man and its Cure With Biotin. *J. A. M. A.* 225: 2199-1200, 1942.

²⁰⁹ Williams, H. H. Clinical Biotin Deficiency. *New England J. Med.* 228: 47-50, 1943.

²¹⁰ Anbar, R. L. p-aminobenzoic Acid, a Vitamin. *Sci. News* 33: 164-165, 1941.

²¹¹ Brandegee, H., Main, E. and Steele, J. M. Effect of Calcium Panthothenate and Para-aminobenzoic Acid on the Gray Hair of Humans. *Proc. Soc. Exptl. Biol. & Med.* 44: 47-49, 1943.

²¹² Javie, B. Clinical Effects of a New B-Complex Factor Para-aminobenzoic Acid on Pigmentation and Fertility. *South. Med. & Surg.* 104: 125-130, 1940.

²¹³ Can Hair Turn White Over Night? *J. A. M. A.* 122: 161-16, 1943.

²¹⁴ Flier, J. J. and Diaz, L. A. Vitamins for Gray Hair. *New York Stat. J. Med.* 43: 1331, 1943.

²¹⁵ Woolf, J. D. W. Nature of Anti Alopecia Factor. *Sci. News* 32: 394-395, 1940.

²¹⁶ Stryker, G. V. and Halbeisen, W. A. Determination of Macrocytic Anemia as Aid in Diagnosis of Certain Deficiency Dermatoses. *Arch. Dermat. & Syph.* 81: 116-13, 1945.

isolated. The human body is unable to synthesize ascorbic acid in the necessary amounts and therefore has to rely on the plant sources especially the citrus fruits, peppers, green leafy vegetables, tomatoes and other plant products.

Vitamin C is easily *inactivated* by oxidation. Cooking, storing without refrigeration, alkalization and the presence of copper even in traces rapidly diminish the content of active vitamin C. In the organism it is concerned with the maintenance of connective tissue. In scorbutic animal the *formation of fibers* from fibroblasts is seriously disturbed and the *fragility of the capillary walls* which in clinical scurvy leads to many manifestations of hemorrhagic disease may be explained by the lack of adequate intercellular substances.¹⁰⁷

Scurvy is at the present time a rare disease. In adults it is seen following malnutrition among inmates of ill managed prisons or other institutions in times of famine or after prolonged gastrointestinal disease with restricted diet. Scurvy is more frequent in infants fed on cow's milk especially if the milk is being sterilized by boiling.

In adults general weakness, pains in the legs, gingivitis, purpura and other hemorrhagic symptoms are the classic manifestations. Undeveloped cases are supposedly common and often mistaken for rheumatism.¹⁰⁸⁻¹¹⁰ Infantile scurvy is clinically characterized by pallor, a worried facial expression, drawn up legs in bed, crying when handled, pains in the legs, subperiosteal hemorrhages especially in the epiphyseal regions and gingivitis with bleeding if the child already has teeth. Anorexia, loss of weight, susceptibility to infection, fever, intestinal disorders, hematuria and epistaxis are other symptoms. Urbach¹¹¹ considers the saturation test for vitamin A deficiency as much more valuable than single determinations of the vitamin A content of blood plasma and urine. This test is based on the observation that the ascorbic acid levels in blood and urine fail to rise substantially and for considerable time in a vitamin A depleted organism after the intravenous injection of 500 mg. of ascorbic acid. In the normal 40 per cent of the injected vitamin is excreted within four hours while in scurvy the excretion is trifling, 20 per cent at the most. The diagnosis is helped by the positive tourniquet (Leede Rumpel) test or a similar method^{112, 113} for testing the fragility of the capillaries. Bleeding and coagulation times as well as blood platelet count are normal.

The blood picture is normal except for a moderate anemia.

The *dermadromes* of scurvy are significant though not specific. The follicular slightly papular dull red hemorrhagic *rash* occurs early in the course of clinical scurvy. Later many of these papules show pronounced intrafollicular keratosis. The rash is symmetrical and occupies predominantly the extensor surfaces of the extremities particularly of the lower legs and the hairy region of the trunk. The palms and soles, the face and the scalp remain free.^{121, 122} Some of the follicular lesions are truly petechial without a papular character. Large subcutaneous extravasations occur in the parts which are subject to friction and

¹⁰⁷Edly W. H. *The Ascorbic Acid* 1937 William & Wilkins Co.
¹⁰⁸Gothlin G. F. Method for Determining Strength of the Skin Capillaries. Indirect Estimation of the Individual Vitamin C Standard. *J. Lab. & Clin. Med.* 28: 441-490, 1933.

trauma such as the popliteal areas and the scalp. Extravasation beneath the conjunctivae also occurs. These dermadromes are more common in infantile scurvy (Möller-Barlow disease).

The papulo hemorrhagic keratotic and follicular rash in scurvy has for a long time been known under various other names like lichen scorbuticus⁷⁸ lichen pilaris or scorbutic gooseflesh⁷⁹. The First World War gave the opportunity for new observations of scurvy on a large scale. In some series the papulokeratotic rash was present in 87 per cent.⁸⁰ The follicular keratoses often affected almost all follicles especially of the anterior aspects of the legs so that a grater like surface resulted. Microscopic features of the scorbutic skin lesions are capillary congestion, interstitial hemorrhage and edema without inflammatory infiltrate. The follicle contains a plug formed of the remnant of the hair and keratotic material. The hair roots are not destroyed.

The follicular lesions in scurvy (Whitfield after Wiltshire⁸⁰) have much clinical resemblance to those in vitamin A deficiency. However the vascular factor which is so pronounced in scurvy is lacking in phrynoderma. Scheer and Keil⁷⁹ therefore believe that the follicular keratoses in scurvy are not due to a multiple deficiency. In experimental vitamin A deficiency in man follicular keratotic papules and perifollicular petechiae were among the first symptoms.^{2, 81} Ecchymoses and gingivitis followed.

Hyperpigmentation in scurvy has been observed¹³⁷ although it is not yet sure whether it is due only to hemosiderin from the hemorrhagic disease or also to the increased melanin production under the influence of vitamin C deficiency. Ascorbic acid is able at least under experimental conditions to prevent melanin formation (von Szent Gyorgi after Schaaff¹³⁷). In the human skin melanin occurs associated with vitamin C.¹³⁷

Gingivitis in scurvy being an early signal is of great significance. The gums are swollen and bleeding, the papillae being enlarged. In small children the teeth may become submerged under the swollen gingiva. If the scurvy lasts longer the teeth may fall out and the alveolus may become necrotic. It has often been stated that scorbutic gingivitis does not develop in an edentulous mouth.

The healing of wounds is greatly impaired in scurvy^{138, 8} at least in part due to the disturbed production of intercellular substances.

Untreated and fully developed scurvy is a disease with a high mortality. However if treatment with 200-300 mg of vitamin C is administered daily either orally or parenterally together with a full diet surprising recovery may be seen. Cordon and Sevringhaus¹³⁹ state that in all the field of medicine there is probably no more dramatic or gratifying result from a therapeutic measure than that which occurs when a patient with scurvy is given an adequate amount of ascorbic acid.

¹³⁷ Jeger R S. Histopathological changes in the skin in scorbutic disease. In: Hirschwald, 1893. A. Hirschwald.

⁷⁸ Kee M and Keil H. Follicular Lesions in Vitamin A and C Deficiency. Arch. Dermat. & Syph. 30: 177-18, 1934.

⁷⁹ Wiltshire H. Hyperkeratoses of the Hair Follicles in Scurvy. Lancet 2: 564, 1919.

⁸⁰ Crandon J H, Lund C C and Dill B B. Experimental Human Scurvy. New England J. Med. 223: 353-360, 1940.

⁸¹ Bartl H M, Jones C M and Ryan A E. Vitamin C and Wound Healing. Experimental Wound in Guinea Pigs. New England J. Med. 226: 469-473, 1942.

No relationship between the level of vitamin C in the blood and the development of a variety of skin diseases altogether 181 cases was found²²² and no curative effect was noticed.²²⁴ Effects on *collod milium*²²⁵ and on *toxicodeimas* from arsphenamine²²⁶ mercury²²⁷ gold²²⁸ have been reported. Some evidence is available that vitamin C exerts a detoxifying influence on arsphenamine treatment and thus may be able to prevent toxic reactions.²²⁹

²²²Lever W. E. and Talbot J. H. Role of Vitamin C in Cutaneous Diseases Arch Dermat & Syph 42 657-663 1940

²²³Latane J. and Branstetter J. Vitamin C and Skin Diseases Acta dermat venereol 38 66 1939 Abstr Arch Dermat & Syph 48 263

²²⁴Way H. C. Collod Milium a Vitamin D Deficiency Arch Dermat & Syph 48 1145 1155 194

²²⁵Dainow I. Dose Utilizing Effect of Ascorbic Acid (Vitamin C) Curative Effect in Salvarsan and Gold Intolerance Ann Dermatol Syph 6 430 437 193

²²⁶Takahashi H. and Uragami M. Klinisch Anwendung von Vitamin C gegen verschiedene Dermatosen Jap J Dermat & Syph 12 133 193 J1 68 23

²²⁷Hamber G. Vitamin C or Ascorbic Acid of the Skin J Dermat 81 103 1942

²²⁸Ishiri K. D. Relation of Blood Ascorbic Acid Concentration to Arsenical Intolerance in Syphilotherapy Brit J Dermat 55 134 19 1943

CHAPTER XXXII

DISORDERS OF THE BLOOD AND BLOOD FORMING ORGANS

(Lymphoblastomas and Allied Disorders)

Leukemia lymphosarcoma Hodgkin's disease mycosis fungoides and the subvarieties of these disorders are now—at least in America—commonly grouped together under the name of lymphoblastomas²²⁹⁰ This term which is not much used in other countries is based on the conception that all these diseases have tumorlike features and that they are related by a common characteristic cell the lymphoblast or a derivative of this cell A great number of transitional cases have been described to corroborate the close relationship^{2291 2292} The neoplastic features are found in the continuous and uncontrolled proliferation of cells which tend to differentiate like their cells of origin The proliferation is infiltrating and is devoid of an orderly structural arrangement No cause is known The course is invariably fatal no certain phenomena of immunity or protection are known²²⁹³ Heredity plays a role²²⁹⁴

Other authors²²⁹⁵ produced some evidence for the infectious nature of the group Spread of the disease from a portal in the lymphatic tissues of the gastrointestinal and respiratory tract inflammation necrosis fever and some experimental facts can be interpreted in favor of an infectious possibly virus²²⁹⁶ etiology Possibly in future a conception of infectious neoplasm will evolve

The term lymphoblastoma as a generic term has been accepted by authors who do not approve of the merging of the entities in question since they consider the differentiating characteristics of greater importance²³⁰¹

Leukemia^{2290 23 265}

Leukemia is a fatal disease of unknown etiology primarily involving the blood forming organs i.e. the bone marrow the spleen the lymphatic nodes

²²⁹⁰Kelvin H L Lymphoblastomas Their Interrelationships Arch Dermat & Syph 11 533 534 1929

²²⁹¹Krumphaar F B Hodgkin's Disease Its Present Status University of Wisconsin Symposium on Blood pp 144 166 1939

²²⁹²Warthin A S Relationships of Hodgkin Disease to Leukemia and Leukemic Lymphoblastoma and Mycosis Fungoides Ann Surg 93 153 161 1931

²²⁹³Fraser J F Mycosis Fungoides as a Variety of Lymphosarcoma Arch Dermat & Syph 11 4 5-445 1935

²²⁹⁴Fraser J F Mycosis Fungoides Its Relation to Leukemia and Lymphosarcoma Arch Dermat & Syph 12 814 5 1935

²²⁹⁵Wile L J and Stiles F Jr Chemical Mutations I Lymphoblastomas JAMA 104 530 537 1935

²²⁹⁶Apitz J Di Leukämien als Neubildungen Virchow's Arch Pathol Anat 299 1-69 1937

²²⁹⁷Wiley M Principles of Pathologic Histology Philadelphia 1914 W B Saunders Co

²²⁹⁸Warthin A S The Reality of Leukemia (in Wiley) Am J Cancer 15 1361 1366 1931

²²⁹⁹Kelvin H L Cutaneous Lymphoblastomas Clinics 3 866-895 1914

²³⁰⁰Forsyth G E Leukemia and Allied Disorders New York 1939 The Macmillan Co

²³⁰¹Ormsby O S and Finckel C W Mycosis Fungoides Arch Dermat & Syph 27 631-64 1933

²³⁰²Hadji N H L Hematology Philadelphia 1933 Lea & Febiger

²³⁰³Rosenthal N and Harri W Leukemia Diagnosis and Treatment JAMA 104 702 706 1935

and the reticuloendothelial cells. It is characterized by widespread rapid and disorderly proliferation of the white blood cells and their precursors. Almost without exception, either during the entire course or in some phase of the disease the white blood count is high, sometimes very high. The appearance of immature leukocytes in the blood, often in very large numbers, is particularly significant. This proliferation of white cells almost always involves only one of the three types, the lymphocytes, the granulocytes, or the monocytes. This is surprising considering the adjacency of the mother cells in the bone marrow and in other organs. The resulting three main types of leukemia, the lymphoid, the myeloid, and the monocytic, are clinically quite different. Generalized enlargement of the lymph nodes is typical of lymphoid leukemia, but some lymphadenopathy may be present in the other types. The spleen is usually enlarged, the very large sizes being found in myeloid leukemia. In monocytic leukemia gangrenous and hemorrhagic lesions of the mucous membranes often dominate the picture. Weakness, dyspnea, fever, and anemia occur in all types. A hemorrhagic tendency is an early and common feature in all types. The metabolic rate is frequently increased. In two out of three cases the disease takes a chronic course over years, with or without remissions. The acute disease ends fatally in a few weeks or months, often with hemorrhagic and mucosal symptoms. Acute course is known to occur in any of the three types. Approximately one half of the myelocytic and of the monocytic cases, but only one fourth of the lymphocytic cases, are acute.^{31, 32}

The leukemias are relatively rare diseases. They constitute a little more than one half per cent of the necropsy diagnoses in a large American series (Ikeda after Forkner³⁰⁰) with about two cases of lymphoid leukemia to one case of myeloid leukemia. This ratio among the necropsies differs materially from that of hospital admissions. Among 455 cases of leukemia treated in Mount Sinai Hospital in New York roughly 66 per cent were myeloid, 28 per cent lymphoid, and 15 per cent monocytic. In Denmark roughly one out of 50,000 persons dies of leukemia per year (Nielsen after Forkner³⁰⁰). No age is exempt, but the fourth decade of life has the largest incidence. The male patients outnumber the females two to one.³⁰¹

Dermadromes Especially of Lymphatic Leukemia—Cutaneous lesions occur in all types of leukemia. It is customary to distinguish between specific skin lesions which histologically consist of the same cells which are characteristic of the blood in the case in question, and nonspecific dermatoses which are often seen in leukemia but do not contain leukemic elements.

The border line is not very sharp, since originally nonspecific lesions may finally become pervaded by the leukemia cells. Even grossly normal skin may prove to harbour specific infiltration. The nonspecific group is often called leukemids³⁰ or just *ids*. The term leukemid has become misleading since

³¹ Friedman, A. B. and Meyer, L. M. Observations on Over 100 Cases of Myelogenous and Lymphatic Leukemia. *Pathology* 11: 341-343, 1945.

³² Autry, C. Sur les leucémides. *Bull. Soc. franç. d. dermat. et syph.* 13: 115, 121, 190.

in analogy to the 'rashes' in infections it suggests the specific and not the non-specific type e.g. syphilids trichophytids etc (see discussion to Sweitzer³⁰⁹). The term 'accompanying dermatoses' (Hautbegleiterscheinungen³¹⁰) has not found approval in the Anglo Saxon literature. The adjective toxic has also been used to characterize these dermatoses. It implies an etiology which has not been proved. It seems best to speak of specific and nonspecific dermadromes. There is no dermadrome which in a clinical sense is absolutely characteristic of one or the other types of leukemia. The majority of published cases of skin lesions belongs to the chronic lymphoid leukemia³¹⁰⁷. However in an analysis of the cutaneous aspect of 160 cases of leukemia³⁰⁸ the incidence was about equal in both main types. Specific infiltrations were more common in lymphoid leukemia (8.3 versus 5.5 per cent). The cutaneous involvement in monocytic leukemia seems very high (75 per cent) but only small numbers are so far available. The diagnostic difficulties in skin leukemia are considerably increased by the experience that the cases with leukemic skin manifestations are frequently subleukemic or aleukemic in the blood³⁰⁷. They often show a leukemic blood only in late stage of the disease. Another difficulty may be created by lymphocytomas. These are infiltrations or tumors which histologically resemble leukemia but remain localized.

Non-Specific Dermadromes—These are variable. In their monograph Arzt and Fuhs³⁰⁹ mention dermatitis eczema erythema exudativum multiforme urticaria purpura and bullous and rupial eruptions. This coincides with Nanta's remark that there are so many combinations in this group that if one would like to go into grouping every single observation could represent a type of its own. The incidence is probably higher than fifty per cent. minor skin lesions often passing unnoticed or at least unrecorded in the medical wards. Pruritus for instance sometimes without any visible skin changes which seems to be the most common symptom, was recorded only in three per cent of the leukemia cases of Epstein and MacEachern³¹⁰⁸. Most authors agree that severe itching alone or in connection with visible rash is a frequent symptom³¹⁰⁹.

Purpura of varying degrees is also common in leukemia. In large series^{3107, 3110} it exceeds the other leukemic rashes. This is not surprising in view of the thrombopenia and hemorrhagic tendency in the leukemias. Chronic urticaria^{3110, 3111} has quite often been described. It is related to Buschke's prurigo lymphatica. This is a violently itching widespread not too dense eruption of small papules which soon become scratched and crusty or impetiginous. The lesions may form

³⁰⁹Switz E. S. E. Leukemid Arch Dermat & Syph 23 109 1023 1939

³¹⁰⁷Gotttron H. Zur Leukämie der Haut Med Film 22 373-377 404-405 1937

³¹⁰⁸Epstein I. E. and MacEachern I. Dermatologic Manifestations of the Lymphoblastoma Leukemia Group Arch Int Med 60 967-975 1937

³¹⁰⁹Arzt L. and Fuhs H. Hauterkrankung n bei Leukosen und Leukoblastomen sowie verwandten Zuständen Handb d H n Gk 1 1929

³¹¹Conbleet T. and Murphy E. L. Lymphatic Leukemia (Chronic) Leukemia Cutis Arch. Dermat & Syph 24 643-645 1933

³¹¹⁰Cavanaugh J. M. Lymph blastoma Arch Dermat & Syph 23 387 1931

³¹¹¹Schreier C. H. Ein Fall von chronischer lymphatischer Leukämie ohne Milz oder Mandel geschwulst aber mit Urticaria. Med Rev 83 430-43 1936 Zbl 83 545

³¹¹²Grassi A. Osservazioni di leucemia leucemica Arch Ital di dermat sif 7 537-611 1931 Zbl 47 9

small erosions and ulcers which leave pigmented spots and streaks. Thus a mottled melanoderma may ensue which resembles the so-called vagabond's skin. The frequent loss of body hair in this stage is not only due to the rubbing off but also to a beginning specific infiltration around the hair follicles.²¹¹ Total alopecia has been observed. The histologic picture is as a rule not a typical leukemic one but surprising specific findings have become known demonstrating that there is no sharp borderline between the specific and nonspecific dermatromes.^{212, 213} The same is true of the herpes zoster which occurs quite often in the course of leukemia.²¹⁷ While the zoster may take a normal course its scars may later become the sites of specific leukemic infiltrations.^{215, 216} Such provocations of specific leukemic lesions by local inflammation or trauma interpreted as Koebner's phenomenon have been observed in many cases after local trauma like insect bites, burns, cupping, piercing of the earlobe, pinching of the ear and other local mechanical injuries.²¹⁸ Aberrant or generalized zoster eruptions which are quite rare seem to occur more frequently in leukemia.^{219, 220} The rare connection of zoster and chicken pox in adults and also the varicelliform eruptions (H. R. Loewer in discussion to Barre^{221, 222}) have been observed several times in leukemic patients. The generalization of zoster seems to occur especially in persons whose resistance has been weakened by disease or age.^{223, 224} Evidence of involvement of the corresponding spinal ganglion by hemorrhage or leukemic infiltration is on record.²²⁵ Some of the zoster eruptions in leukemia may have been caused by arsenical

Specific Leukemic Dermatromes—Specific leukemic dermatromes appear in several types which notwithstanding their different clinical aspect have

- ²¹¹ Sauts A. Les troubles l'appareil hématopoïétique (Hématodermies). Nouvelle Pratique Dermatologique vol 5 pp 51 ff.
- ²¹² Arzt L. Leukämische Lymphomatose. Zbl 49 57.
- ²¹³ H. Raccini G. Über eine noch nicht beschriebene Hauterkrankung (Rupia) im Verlaufe der chronischen Leukämie mit lymphatischer Leukämie. Dermat. Wechschr 90 741 49 1931.
- ²¹⁷ Carver L. F. and Isaacson J. D. A Note on the Occurrence of Herpes Zoster in Hodgkin's Disease Lymphosarcoma and the Leukemia. Am J Clin 16 50 514 1937.
- ²¹⁸ Isaacson J. Haut Leukämie in Zoster Reiten. Zbl 22 17.
- ²¹⁹ Isaacson J. Herpes Zoster und varicellenartige Eruptionen bei lymphatischer Leukämie. Zbl 20 23.
- ²²⁰ Hille H. Zoster bei Leukämie. Prokation leukämischer Infiltrate in der Haut. Arch f Dermat u Syph 139 34 10 1930.
- ²²¹ Barre F. Zoster bei Leukämie. Arch f Dermat u Syph 164 561 61 1931.
- ²²² Barre F. Marquet J. Herpes zoster généralisé chez un Leukémique. Arch f Dermat u Syph 176 35 304 1937.
- ²²³ Carver L. F. and Isaacson J. D. Cuti leukämische Lymphomatose mit Herpes Zoster generalisatus. Zbl 22 544 1930.
- ²²⁴ Barny R. F. Cuti leucemia (cutis resembling Herpes Zoster) in Leukemia. Arch f Dermat u Syph 25 1130-1151 1931.
- ²²⁵ Barny R. F. Zosteriform Leukemia (cuti). Arch f Dermat u Syph 37 234-246 1934.
- ²²⁶ Jara G. W. and Vogt H. Zur Frage der Hautleukämie. Deutsches Arch f klin Med 185 6 1940.
- ²²⁷ Isaacson J. D. Zoster generalisatus bei lymphatischer Leukämie. Deutsches Arch f klin Med 182 103.
- ²²⁸ Barton R. L. and O'Leary I. A. Herpes Zoster Generalisatus Associated With Chronic Lymphatic Leukemia. Arch Dermat u Syph 51 263 65 1915.
- ²²⁹ Lutz W. Skin Diseases in Relation to General Organism. Review of Literature Dermatologi 82 177 186 1911.
- ²³⁰ Hildad (Phy) A. and Hiltner I. Varicelliform Leukämie her Lymphadenose. Arch f Dermat u Syph 168 517 519 1934.
- ²³¹ Freund H. Zoster und Leukämie. Arch f Dermat u Syph 154 4 6-489 1928.

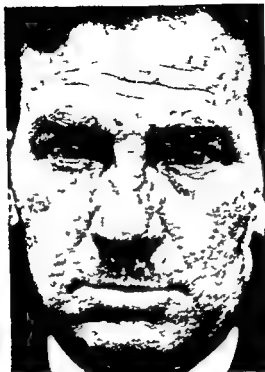


Fig 30 —Lymphatic leukemia specific papular eruption (Courtesy Dr. M. Jenner)

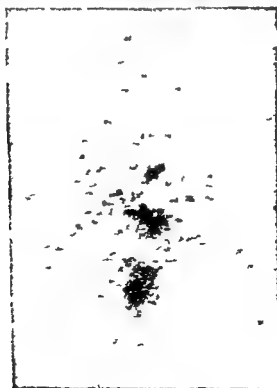


Fig 30b Lymphatic leukemia skin eruption (Courtesy Dr. M. Jenner)

a common histopathology—the leukemic infiltration. The rarest of the specific leukemic involvements of the skin is the generalized papular rash which has great similarity to a secondary syphilitic exanthema. The dense²³¹³ eruption of small red mostly follicular papules favors the trunk especially the hips leaving the face and the limbs relatively free. Considering its great rarity the diagnosis



Fig. 307. Specific papular eruption in lymphatic leukemia. (Courtesy Division of Dermatology Department of Medicine University of Chicago.)

of leukemia will hardly be made from the rash alone. But after exclusion of syphilis and other papular exanthemas e.g. drug eruptions leukemia should be considered^{2312, 2313}. This diagnosis will be much easier if the papules tend to coalesce and form plaques or if some papules reach tumor size. Such cases of tumors arising from beds of papules link the papular type of cutaneous leukemia with the leukemic tumors. Another transition is the furunculosis resembling rash of large not very distinct papules of moderately dense distribution²³¹⁴.

The *cutaneous tumors* in leukemia^{2313, 2314} have been seen in sizes varying from a pinhead to a large potato. They are oval or round mostly raised. If they are

²³¹²Arzt L. Prurigo Lymphatica Zbl 54 71

²³¹³Remenovsky. Lymphatische Leukämie mit spezifisch papulösem Exanthem und bullöser Eruption Zbl 51 85

confluent the lines of coalescence are sometimes recognizable by deep linear grooves. Their color may be red, bluish, purple, brown, even almost black. Under diascopic pressure they appear brown. The skin over the tumors may be extended, glossy, atrophic with some telangiectases or scaly. The tumors are usually movable. The small tumors are quite hard. The large growths are often described as soft, less often as having the elastic hardness of cartilage. The tendency to spontaneous regression, either by central necrosis or healing with atrophy, is small (Freudenthal after Gottron³⁰⁷) also^{2, 39}. They are almost always painless. The tumors may appear in any region of the body surface.



Fig. 304.—Lymphatic leukemia tumors. (Courtesy Dr. M. Jansen.)

but they have a definite affinity to the soft areas of the face: the eyelids, the lips, the nose, the cheeks, and the ear lobes. There is a certain tendency to symmetric development. Such symmetric tumors may create the most grotesque disfigurement of the human face known to medicine. In such rare but well known cases large bluish bulges hang over the eyes and cheeks obstructing the vision. The nose resembles a proboscis, the ear lobules may be pendulous and elongated. In other cases the tumefaction is more diffuse over the face, resulting in a facies leonina not unlike leprosy. The scalp may also be involved. The penis and prepuce sometimes become the site of leukemic tumors which may seriously interfere with micturition. The nipples, soft areas too, have several times been described as a characteristic site of leukemic tumors^{234, 236}.

Recht E F. Leukemia Arch Dermat & Syph 18: 609, 1904.

Meschli Kraut J M. Circumscribed Leukemia Cutis Arch Dermat & Syph 32: 144, 1935.

Whitehouse W J. Leukemia Arch Dermat & Syph 11: 799-800, 1908.

The mucous membranes of the mouth pharynx larynx nose and eyes may also become involved. Oral lesions of this kind are described as nodular or diffuse infiltrations. A picture of a patient of Milians²⁰¹ shows a lobulated gyrate tumor involving the whole soft palate and covered with petechiae. Such infiltrations of the soft palate have been seen several times.²⁰² Connor describes a similar case in a Negro. There were large flat granulomatous masses practically covering the buccal surfaces on both sides. Smaller tumors were located on the soft palate and on the gums. The masses were dull red the edges overhanging the bases of the ulcers. There was some superficial ulceration in this case but the lack of ulceration is emphasized in other cases. In other instances²⁰³ the infiltrations were smooth and multiple scattered over the entire mucosa of the upper air passages from the lips down to the larynx. In one case a tumor of the epiglottis accompanied by skin tumors proved to be of lymphocytic origin.²⁰⁴

Tumors have been observed in all ages including a seven months old baby²⁰⁵ a three year old boy²⁰⁶ and very old people.

The tumors often grow slowly or remain stationary over long periods even as long as thirteen years.

In some cases the appearance²⁰⁷ of cutaneous tumors coincides with a change of a chronic course to an acute phase of leukemia with more numerous immature cells in the blood.²⁰⁸

The diagnosis of the leukemic tumors is easy in fully developed cases. But difficulties which can only be overcome by repeated biopsies may arise if there is only one small nodule²⁰⁹ or if the lesion resembles other tumors e.g. ulcerated epithelioma²¹⁰ melanoma²¹¹ hemangioma²¹² or neurogenic sarcoma (author's case). Blood count and biopsy will finally secure the diagnosis but it should be remembered that large tumors of the skin may be found in an aleukemic phase of the disease.²¹³

Generalized Exfoliative Erythroderma This complication of leukemia is very rare. Epstein and Mieschachern²¹⁴ saw one case in 60 cases of chronic lymphoid leukemia and not a single case in 90 cases of myeloid leukemia. It is about five times rarer than the other dermatomas of lymphoid leukemia.

¹⁹¹ Theodorowicz A. and Maticek A. Lymphatisch Leukämie mit Hauterkrankung. Zbl. 40 1934

¹⁹² Mar. H. Leukämie cutis mit Beteiligung des Rachens und des Kehlkopfes. Ztschr. f. Laryng. Rhin. 19 202 204 1930

¹⁹³ McCafferty. Lymphoma. Arch. Dermat. & Syph. 29 433 435 1939

¹⁹⁴ Stalling. Fall 5. Ein Fall von Hauttumor und myeloid. Reaktion im Blut. Medizinische Grenz. 11 719 730 1930 Zbl. 35 634

¹⁹⁵ Simon. H. Leukämie cutis. Proc. Roy. Soc. Med. 1031 1033 1930

¹⁹⁶ Emile. Wall J. & H. Lach. Wall J. Leukämie cutis. Ann. 5 513-5 1931

¹⁹⁷ Zelsler. E. and C. A. M. R. Lymphatic Leukemia of the Skin. Arch. Dermat. & Syph. 26 222 1931

¹⁹⁸ Busch. A. Lymphatische Leukämie. Zbl. 41 294

¹⁹⁹ White. C. J. Leukemia Cutis. Resembls Epithelioma. Arch. Dermat. & Syph. 26 51 1931

²⁰⁰ Gray. A. M. H. Leukemia cutis. Proc. Roy. Soc. Med. 22 1641 1642 1930

²⁰¹ Rosenthal. R. L. Lymphatic Leukemia. Arch. Dermat. & Syph. 26 67 1931

²⁰² Throne. B. Lymphatic Leukemia. Arch. Dermat. & Syph. 26 506 1931

²⁰³ Zim. Herman. F. F. and Curtis. H. C. Aleukemic Myelosis With Cutaneous Nodules. Arch. Dermat. & Syph. 33 644-659 1936

The condition may precede the blood changes for years³⁵⁰ or it may develop in any stage of the leukemic process. It may develop secondarily to a specific papular rash or specific nodules^{351 352} or nodules or tumors may follow the diffuse reddening of the skin³⁵³. In other cases the universal involvement of the skin was ushered in by swelling and erythema of some regions mostly the groin and armpits^{354 355} or by bullous eruptions suggesting pemphigus³⁵⁶. In some instances excessive perspiration was an initial symptom³⁵⁷. Pruritus was almost always severe and continued so throughout the course of the disease. The variety of pictures seen in the initial stage of the disorder is in remarkable contrast to the uniformity of the later stages.

The entire body surface is red sometimes bright red sometimes dusky or purplish. The skin is often thick and leathery hardly pliable. While the small wrinkles are mostly flattened the large folds are the more deepened. The loss of pliability expresses itself in painful fissures especially on the hands. The exfoliation varies from slight branny scaling to the shedding of large sheets of dry epidermis. In some cases vesicles crusts and oozing create the impression of a generalized eczema. Nodules or plaques are sometimes found in the erythroderma. The axillary and pubic hair is shed early or rubbed off the hair of the bearded area and of the scalp follows^{358 359 360}. The ground off concave edges of the nails and their glossy surfaces tell of constant rubbing and scratching. Later on they are often dystrophic thickened opaque brittle and discolored.

The superficial lymphatic nodes are all swollen the lack of axillary and pubic hair making them more visible. The patient is very uncomfortable. The rhagades the pruritus the ectropion which usually develops complicating pyodermic infections chilliness and the weakness and depression caused by the severe disease create a horrible syndrome of suffering. The course may drag on over many years. In the later stages the infiltrated skin may become atrophic³⁶¹. Leukemic erythroderma is usually not influenced by any treatment including radiation.

The fatal outcome is frequently precipitated by bronchopneumonia

³⁵⁰Coyne J A and Frieto J O. Erythrodermische Form der akuten Leukämie. *Archiv für Dermatologie* 1916; 2: 256-262. Zbl. 111: 76.

³⁵¹Hollmann J. Erythroderma als Folge einer chronischen lymphatischen Leukämie mit Erythroderma. *Archiv für Dermatologie* 1933; 77: 394-397. Zbl. 111: 469.

³⁵²McCarthy P J. Erythroderma lymphaticum exudativum. *Archiv für Dermatologie* 1913; 110: 116-123.

³⁵³Ballou H and Davis L. Leber's case of Erythroderma and acute lymphatic leukemia. *Dermat. Wochenschr.* 1910; 11: 110-117.

³⁵⁴Wich von H. Leukämie Cutis. *Arch. Dermat. & Syph.* 22: 145-149. 1910.

³⁵⁵McCarthy P J. Raynaud's Disease (Possibly Due to Chronic Arteriole Disease). *Arch. Dermat. & Syph.* 23: 75-79. 1913.

³⁵⁶Maréchal J. Rimaud P and Hoch J. Erythrodermie comme manifestation clinique initiale et pendant quelque temps exclusive d'une leucémie à élimination primitive d'évolution ultérieure. *Bull. Soc. française de dermat. & syph.* 42: 1503-1510. 1933.

³⁵⁷Ma Corma H. Leukämie F. Erythrodermia. *Proc. Roy. Soc. Med.* 21: 1171-1174. 1914.

³⁵⁸Arnold J. Chroische lymphatische Leukämie mit Lymphomato de Haut. *Arch. f. d. ges. Med.* 30: 412-417. 1923. Zbl. 111: 28-29.

³⁵⁹Theodorowicz A. Quatre cas d'érythrodermie leucémique. *Bull. Soc. française de dermat. & syph.* 1919; Zbl. 111: 33.

Chronic Myeloid Leukemia—Skin manifestations of chronic myeloid leukemia being much rarer than those in lymphoid leukemia are not yet well enough known to insure a definite type. Hardly more than fifty cases have been published. All the dermatomes observed in chronic lymphatic leukemia have been seen in the chronic myeloid type too. Nonspecific hemorrhagic²⁹⁰



Fig. 309



Fig. 310

Fig. 309—Chronic myeloid leukemia. Specific cutaneous tumors. (From Paul J. T. and Limalat L. R. Arch. Dermat. 1942.)

Fig. 310—Chronic myeloid leukemia. (From Paul J. T. and Limalat L. R. Arch. Dermat. 1942.)

urticarial pruriginous rashes^{291, 292} as well as infiltrations, plaques²⁹³ and tumors are known.²⁹⁴ The impression prevails that there is less tendency for the tumors to develop in the soft parts, especially in those of the face. The facies leonina which is so striking in some cases of lymphoid leukemia has not yet become known in myeloid leukemia. The tumors seem to occur more frequently on the trunk.^{295, 296} The extremities have only occasionally been found to be involved.

²⁹⁰ Martenstein H. Multipel Hauttumoren bei chronischer Leukämie. Zbl. 85. 98. 1937.
²⁹¹ Nakam L. Les manifestations cutanées de la leucémie myéloblastique chronique. Bull. Soc. franc. de dermat. et syph. 88. 1236. 1^{er} 4. 1937.

²⁹² Haden R. L. Leukemia Cutis (Myeloblastic). Arch. Dermat. & Syph. 37. 870-871. 1938.

²⁹³ Paul J. T. and Limalat L. R. Specific Cutaneous Lesions in Chronic Leukemia. Arch. Dermat. & Syph. 45. 697-905. 1942.

(Aubertin's case in a picture shown by Nanta³¹⁴ Hollander³¹⁵ and others) Telangiectases on and around the tumors are especially mentioned by various authors^{309 323a}

There seems to be a more marked tendency to hemorrhage, necrosis and ulceration in the myeloid tumors particularly in those of the mouth^{365 368} than in the corresponding lymphoid lesions



Fig. 311 — Chronic myeloid leukemia. Specific infiltration surrounding sweat gland. (From Paul J. T. and Limatzi L. R. Arch. Derm. 1942)

Monocytic Leukemia—Monocytic leukemia³⁶⁷ constitutes only a small fraction of the leukemias^{302 309 365}. But it is likely that cutaneous and oral involvement is relatively frequent in this type (three out of four cases of the series of Epstein and MacEachern³⁶⁸)

While so far no specific clinical picture different from the other leukemic dermadromes has evolved the frequent occurrence of exfoliative dermatitis is remarkable. Purpuric and bullous lesions are often encountered in early stages and so are indurated eczematoid plaques resembling the premalignant stages of

³¹⁴Hollander L., Kastlin B. J., Lerman H. H. and Schmitt C. L. Myeloid Leukemia With Cutaneous Manifestations. Arch. Derm. & Syph. 29: 821-834, 1934.

³¹⁵Richter W. Myelotisch Leukämie mit Hautmanifestation unter dem Bilde eines Abszesses. Zbl. 44: 372.

³¹⁶Gotttron H. Perakute Myeloblastenleukämie. Zbl. 39: 495, 1931-193.

³¹⁷Schilling K. V. Blutakute Leukämieformen. Verh. II 37. Kong. deutsch. Ges. inn. Med. Wiesbaden 1935.

³¹⁸Doan G. A. and Wiseman B. S. Monocytic Monocytoids and Monocytic Leukosis. Ann. Int. Med. 8: 343-416, 1931.

mycosis fungoides^{269, 270} Shotty papular²⁷¹ nodular or tumorous discrete or coalescent eruptions have become known²⁷² The lesions may be either superficial or deep seated creating sarcoid pictures Their development seems to be faster and their tendency to spontaneous regression more marked than in the other leukemic tumors Ulceration²⁷³ is considered ominous²⁷⁰ As in the other leukemias the cutaneous changes may precede accompany or follow the



Fig. 31.—Monocytic leukemia (Courtesy Division of Dermatology Department of Medicine University of Chicago)

blood changes The dermatological diagnosis of monocytic leukemia can only be established by biopsy and in connection with other clinical findings² since the cutaneous picture may resemble all other lymphoblastomas

²⁶⁹ Loveman A B Monocytic Leukemia Cutis South M J 29 2 7-364 1936

²⁷⁰ Montgomery H and Watkins C H Folliculitis Dermatitis as Manifestation of Monocytic Leukemia Schilling Miesota M d 21 636-641 1934

²⁷¹ Mercer H T The Dermatoses of Monocytic Leukemia Arch Dermat & Syph 31 615-635 1935

²⁷² Freeman H E and Kolitzky G Cutaneous Lesions in Monocytic Leukemia 2 Cases Arch Dermat & Syph 40 218-240 1939

²⁷³ Lynch F W Cutaneous Lesions Associated With Monocytic Leukemia and Reticulo-Endotheliosis Arch Dermat & Syph 34 775-796 1936

Chloroma—In contrast to the earlier literature chloroma is now considered a variant of myeloid leukemia originating from the marrow especially of the cranial bones and taking the course of a highly malignant tumor. The name (green tumor) characterizes the green color of the lesions produced by a lipid probably iron containing substance. Two main clinical types of chloroma occur.²¹⁷⁴ In the juvenile cases a rapidly growing orbital tumor produces exophthalmus and finally profound proptosis. Cranial tumefaction with a great variety of symptoms lymphadenopathy gross involvement of other bones and severe anemia follow. In the much rarer adult type the course resembles acute leukemia complicated by gross bony involvement.

Since the arrival of the modern methods of hematology myeloid leukemia has been found to be present almost constantly. Autopsy reveals green foci of myeloid tissue throughout the body.

Severe anemia with a green hue and petechial purpura and varying macular or papular rashes¹⁰⁰ and tumors³⁷⁵ have been described mostly in children. Dense nodular greenish rashes in adults are known. Similar to other acute leukemias ulcerative gingivitis and easily bleeding infiltrations of the base of the tongue and of the tonsils occur. In contrast to the oral lesions of other leukemias these lesions are green in color.



Fig. 313.—Foci of myeloid tissue in acute lymphatic leukemia.

Acute Leukemia—Acute leukemia occurs about half as often as chronic leukemia and four out of five acute cases belong to the myeloid type.²³⁰² Acute leukemia²¹⁸ usually starts with enlarged tonsils stomatitis and/or upper respiratory infection of more than usual persistence and severity. Hemorrhages from mucous membranes particularly of the nose and gums are an early symptom which persists throughout the disease. Anemia develops rapidly. Splenic

²¹⁷⁴ Kaul F A. Chloroma. Arch Int Med 59: 691, 1937.

²³⁰² Morrison M, Samuels A A and Rullitt R I. Congenital Leukemia With Chloroma. Am J Dis Child 48: 33-33, 1939.

²¹⁸ Foerster C F. Acute Especially Monocytic Leukemia. Arch Int Med 52: 1-34, 1934.

enlargement often causes abdominal tenderness. Due to the increasing hemorrhagic diathesis bronchopneumonia or sepsis death ensues within four weeks or less in 60 per cent of the patients and within eight weeks in 84 per cent.²²⁷ None of 113 cases lived longer than twenty six weeks.

The white cells which dominate the blood picture with usually over eighty per cent are uniform and immature mostly myeloblasts less often lymphoblasts or monoblasts. The blood platelets run low and the coagulation and bleeding times are prolonged. The absolute number of leukocytes may be about normal. Leukopenia is common in the early stages.

Skin and Mucosal Manifestations — Lorkner²²⁸ emphasizes the importance of initial gingivitis as an aid in differentiation of the acute leukemias. It is most marked and diffuse in monocytic leukemia. Here it may extend to the pharynx usually causing ulceration and bleeding. More than in the other types a diffuse cellulitis is apt to appear about the lesions causing tooth ache and painful acute inflammation in the deeper tissues of the face. The patients are usually first seen by a dentist. If teeth are extracted the bleeding is severe and some times fatal. Deep necroses have followed such extractions. Several authors emphasize the submerging of the teeth in the swollen pale pink soft and tender gums which bleed easily.^{229, 230} The oral aspect sometimes resembles scurvy. Besides the gingivitis gangrenous punched out ulcerations in the floor of the mouth occur. The necrotic character of the leukemic infiltration may dominate the changes in the tonsils and the lymphoid tissues of Waldeyer's ring.²³¹ Non-resembling pictures may ensue.^{232, 233}

The nonspecific as well as the specific skin manifestations in acute leukemia are essentially the same as in the chronic cases. However the nonspecific eruptions seem to have a purpuric tendency and the specific leukemic lesions show a greater tendency to regressive changes like central softening ulceration necrosis and gangrene. This is illustrated by the observations of severe necroses after minor operations performed on acutely leukemic patients. The deep and wide necrosis after the application of a vesicant (Leube and Fleischer'ster Arzt and Fuhs²³⁴) belongs here too. The morphology follows the familiar patterns of papular rashes,²³⁵ nodules, tumors, plaques and erythroderma.²³⁶

²²⁷Warren, A. L. Acute Leukemia. *Am J M S* 4: 273 490 500 1919

²²⁸Fitzgerald, L. J. Oral Lesions in Leukemias. *J Iowa M Soc* 32: 473-476 1943

²²⁹Janacek, J. G. Abbott, C. A. and Werrer, R. D. Leukemic Gingivopathy. Case of Acute Aleukemic Leukemia. *J Am Dent A* 29: 1123 1127 1919

²³⁰Osgood, E. E. Monocytic Leukemia. Report of 6 Cases and Review of 127 Cases. *Arch Int Med* 109: 931 951 1937

²³¹Hirz, A. Klinische Beobachtungen bei der Lymphogranulomatose. *Wien Arch f Inn Med* 24: 477-484 1934

²³²Karl, W. Acute Myeloblasten Leukämie. *Zbl B* 54: 7

²³³Cohen, I. Cutaneous Tumors in Acute Myeloid Leukemia. Nederl Tijdsch v geneesk pp 1051 1053 1936. *Zbl B* 1: 2

²³⁴Eppstein, T. Fall von akuter aleukämischer lymphatischer Leukämie mit ausgedehnter spezifischer Hautveränderung. *Festschr f Bfla Entz* pp 4 40 1914. *Zbl B* 59: 662 1929

²³⁵Guldberg, F. Zur Klinik der Leukämia cutis. *Venerol* 7: 33-37 1930. *Zbl B* 709 1031

²³⁶Zimmermann, O. Zur Kasuistik der Erythämie mit Leberrang in Leukämie. *Klin Wchnschr* 13: 696 699 1934

The histology of leukemic lesions of the skin and mucous membranes is of marked uniformity. There is a more or less dense infiltration of the superficial or deep layers of the cutis composed of the characteristic leucocytes. The infiltrates often form perivascular sheaths but in fully developed lesions the accumulation of cells throughout the dermis is so dense that the perivascular arrangement disappears.

Hodgkin's Disease

Lymphogranulomatosis (Paltau and Sternberg)

Hodgkin's disease is a chronic disorder of the lymphatic system. It starts in sixty five per cent of the cases with the painless enlargement of cervical lymph nodes. Gradually other groups and finally the entire lymphatic system including the spleen and often the liver become involved. The enlarged lymph nodes may become large tumors which cause severe local symptoms especially in the mediastinum. Chronic intermittent fever, weakness, loss of weight, cough, edema, diarrhea, anemia and finally cachexia are the usual features. The blood picture is not characteristic but anemia is common. Eosinophilia is present in 20 per cent and leucocytosis is an occasional finding. The course may be rapidly fatal or slowly progressive over one to rarely more than three years. A few instances of survival for much more than ten years are known.

The disease is most common in the third decade of life but no age or race is immune. Three out of five cases are in men.

Dermadromes—The incidence of skin manifestations in lymphogranulomatosis follows generally the pattern of the other lymphoblastomas. There are nonspecific and specific dermadromes. The former are common and the latter are rare.

Nonspecific Cutaneous Manifestations—The large series vary in their observations on *pruritus* in Hodgkin's disease. Thirty two per cent (Burnams after Baum²²⁷), eighteen per cent²²⁸, six per cent²²⁹ and three per cent (Longcope after Baum²²⁷) are some of the percentages. Especially in France *pruritus* seems to be considered so common that lack of it prompted publication of three cases²³⁰. *Pruritus* is often an early symptom which may precede the lymphadenopathy by as long as two years^{231, 232}. High blood sugar or unexpected high urine sugar

²²⁷Baum F. Atypical Cutaneous Symptoms in Lymphogranulomatosis. Arch. Dermat. & Syph. 174: 418-44 (1939).

²²⁸Burg R. E. and Lehman E. P. 54 Cases of Hodgkin's Disease. Arch. Surg. 63: 832-849 (1941).

²²⁹Oakey R. S. Jr. Hodgkin's Disease. 52 Cases. Hahnemann Monthly 79: 139-149 (1944).

²³⁰Polino H., Zuccoli H. and Recordier M. Trois nouveaux cas d'lymphogranulomatose maligne sans prurit et sans éosinophilie. Gang. 3: 550-554 (1929).

²³¹Ambler J. V. Hodgkin's Disease. Arch. Dermat. & Syph. 25: 1149-1150 (1932).

²³²Waddell J. F. Gangrenous Herpes Zoster in Hodgkin's Disease. Arch. Dermat. & Syph. 29: 734 (1939).

enlargement often causes abdominal tenderness. Due to the increasing hemorrhagic diathesis bronchopneumonia or sepsis death ensues within four weeks or less in 60 per cent of the patients and within eight weeks in 84 per cent.²⁷⁷ None of 113 cases lived longer than twenty six weeks.

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²⁷⁷Warriss H L. Acute Leukemia. *Am J M Sc* 178: 400-500 1910.

²⁷⁸FitzGerald L M. Oral Lesions in Leukemias. *J Iowa M Soc* 33: 44-46 1943.

²⁷⁹Pasterjack J G, Abbott C A and Werne R D. Leukemic Orophathy. Case of Acute Aleukemic Leukemia. *J Am Dent A* 29: 1193-1197 1941.

²⁸⁰Ogden F H. Monocytic Leukemia. Report of 6 Cases and Review of 127 Cases. *Arch Int Med* 109: 931-951 1937.

²⁸¹Hierz A. Klinische Beobachtung bei der Lymphogranulomatose. *Wien Arch f Inn Med* 24: 427-451 1934.

²⁸²Karl W. Acute Myeloblasten Leukämie. *Zbl* 54: 72.

²⁸³Cohen I. Cutaneous Tumors in Acute Myeloid Leukemia. *Nederl tijdschr v geneesk* pp 1051-1053 1936. *Zbl* 54: 172.

²⁸⁴Epstein T. Fall von akuter aleukämischer lymphatischer Leukämie mit ausgebreiteter spezifischer Hautveränderung. *Festschr f Bfä Fntz* pp 4-49 1919. *Zbl* 29: 33-109.

²⁸⁵Sulzberg F. Zur Klinik der Leukämie cutis. *Venerol* 7: 33-37 1930. *Zbl* 36: 60-1931.

²⁸⁶Zimmermann O. Zur Kasuistik der Erythrodermie mit Uebergang in Leukämie. *Klin Wchnschr* 13: 696-699 1934.

especially in children^{298 399} Desquamation and dryness^{300 401} without other characteristics of erythroderma as well as petechiae are often noticed Herpes zoster well known as a dermatome in other lymphoblastomas occurs in lympho granulomatosis too^{329* 402}



Fig 315—Hodgkin's disease. No specific violent itching eruption. Note deep scratches. Subdied after x-ray treatment of metastatic and inguinal lymphatic nodes.

Generalized exfoliative erythroderma may be nonspecific or specific or at first the former then the latter. It occurs in all degrees of severity. Its clinical

²⁹⁸Feer W. Lymphogranulomatose bei Kindern. Jahrb f Kinderh 122: 145-169, 1909.

³⁹⁹Schoenhof G. Die Lymphogranulomatose der Haut. H. dt. I. H. u. Ok. 8: 1, 271-334, 1909.

⁴⁰⁰Podr F. Lymphogranulomatose mit eigentümlichen Verschiebungen der Haut. Orvosokozs. 1210-1: 11, 1909. Zit. 11: 791.

⁴⁰¹Ronchese P. Ichthyiform Atrophy of Skin in Hodgkin's Disease. Arch. Derm. & Syph. 47: 774-781, 1943.

⁴⁰²Pendergrass F. and Lancaster H. K. Herpes Zoster in Hodgkin's Disease. Am. J. M. 9: 188-226-333, 1904.

picture hardly differs from that in lymphoid leukemia^{207,208,209} Ichthyosiform keratosis has been observed²¹⁰

Edema is a feature in advanced Hodgkin's disease. It may involve a vast area or the whole body and be part of the cachexia. Of greater dermatological interest is the localized elephantiasitic edema of the penis and scrotum²¹¹ and of the hands and feet²¹². Melanoderma may reach degrees which suggest Addison's disease. Such pigmentations have been observed in cases without preceding x-ray or arsenic medication²¹³. Hodgkin's disease has several times been seen to develop following unusually heavy pigmentation from sunlight exposure²¹⁴.

Specific Dermadromes—Tumors and Ulcerations—This group includes papular rashes as well as infiltrations and larger lesions which one would be more inclined to call tumors. They are all of the same nature. There is no need to form a separate group of lymphogranulomatous ulcerations of the skin since no ulceration occurs without a preceding tumor.

Papular rashes consisting of more or less densely^{215,216} placed cutaneous papules resemble in their clinical appearance those encountered in leukemia. They may develop from preceding prurigo lymphatica²¹⁷. A difference may perhaps be seen in the more pronounced regressive tendency of the lesions. Erosion, ulceration and healing with scarification or central depression is common^{218,219,220}. The lesions may be situated in varying depths of the cutis and subcutis thus varying in color and palpability. The rash mostly covers the trunk with a certain predilection for the sternal area. In some cases the lesions are grouped together in circinate²²¹ or corymbiform arrangement (Bruusgaard after Schoenhof²²²). The number of such observations however is too

²¹⁵ Schreiber. *Lymphogranulomatose* Zbl 88 507 1934

²¹⁶ Loveman A. H. Cutaneous Manifestations of the Lymphoblastomas. *Hodgkin's Disease* J. A. M. A 104 1843 1846 1935

²¹⁷ Wigley J. E. M. Hodgkin's Disease With Erythrodemia. *Proc Roy Soc Med* 21 81 1934

²¹⁸ Bruck C. Lymphogranulomatose maligna mit eigentlicher Hautveränderungen. *Acta Dermat* 20 593 1930

²¹⁹ Lahe. *Universelle Erythrodermie bei Hodgkinscher Krankheit* Zbl 82 583

²²⁰ Gougeot H. Blum J. Oberlin G. and Filscheff O. Atrophie de l'épiderme et du derme superficiel et desquamation intense généralisée de la peau (sans érythrodermie) dues à une lymphogranulomatose atypique. *Arch dermat-syph* Hôp St Louis 4 349 360 1937

²²¹ Tommasi L. Pityriasis rubra di H. B. a-Jada Sohn in oggetto affetto da linfogranulomatose maligna di Sternberg. *Paltauf Glor Ital di dermat e sif* 71 1240-1244 1930

²²² Capicci M. Di un caso di linfogranuloma Paltauf Sternberg (*Eritrodermia pityrialea tipo Hebra*). *I soli linico (sez med)* 30 355-403 1930

²²³ Tupper G. Lymphogranulomatosis (Paltauf Sternberg) of skin. *Arch f Dermat u Syph* 181 7 700 1941

²²⁴ Aubert Covisa J. and de la Cuesta L. Elephantiasis of Penis and Scrotum in the Course of Malignant Lymphogranulomatosis (Paltauf Sternberg). *Actas dermo-sif* 28 734 738 1936

²²⁵ Paszlay G. Lymphogranulomatosis. Zbl 44 901 193 1933

²²⁶ Riehl G. J. Pigmentierung bei Lymphogranulomatose (Paltauf Sternberg). Zbl 86 5 1937

²²⁷ C. Sham Little E. Lymphogranulomatosis. *Proc Roy Soc Med* 31 1550 1937

²²⁸ Weltner G. F. and Winer L. H. Ulcerative Hodgkin's Disease. *Arch Dermat & Syph* 61 2 236 1945

²²⁹ Nobl G. Juvenile tuberculous Lymphogranulomatose. *Wien klin Wchnschr* 46 717 719 1933

²³⁰ Hersack G. H. Cutaneous Hodgkin's Disease With Terminal Blood Stream Spread. *J. A. M. A* 126 10 510 1944

²³¹ Reil. Lymphogranulomatosis cutis. Zbl 86 507 1937

²³² Dietrich. Lymphogranulomatose der Haut. Zbl 41 669

²³³ Waugh. Hodgkin's Disease. *Arch Dermat & Syph* 21 125 1930



Fig 316



Fig 317



Fig 318

Fig 316 — Papulo-nodular specific eruption in Hodgkin's disease

Fig 317 — Papulo-nodular specific eruption in Hodgkin's disease

Fig 318 — Hodgkin's disease — Papulo-nodular specific eruption and transition in exfoliative erythroderma.

(From Deek R. J. A. M. A.)

small to draw conclusions with regard to an infectious nature. The grouped lesions link with the cases with large tumors in small numbers. A large node or plaque may be surrounded by satellites^{242, 243}. Such plaques may reach hand size or may cover half of the scalp or even half of the chest²⁴⁴ or one groin²⁴⁵. These giant plaques are quite suggestive of Hodgkin's disease and are rarely found in other lymphoblastomas. Tumors of the face²⁴⁶ and of the ear lobes²⁴⁷ sometimes in symmetrical arrangement²⁴⁸ may create a *facies leonina*. Local trauma may be followed by development of tumors. The consistency of the tumors



Fig. 319 - Hodgkin's disease. Ulcerated cutaneous tumor of the anterior chest wall

varies with the depth and the degree of regression and scarring. An uneven firmness is a frequent finding (Wirz after Schoenhof²⁴⁹). The color of these lesions is described as red to dirty yellowish and brown. Most describers emphasize the tendency to ulceration and sinus formation²⁵⁰. The whole giant tumor plaque may become an ulcer with undermined²⁵¹ or infiltrated edges leading to invasion of deeper structures even bones.

²⁴²Greenhaus C. A. and Cornell V. H. Lymphoblastoma (Hodgkin's Disease) of the Scalp. *Case Arch Dermat & Syph* 29: 560-573, 1931.

²⁴³Killand H. H. and Montgomery H. Cutaneous Ulcerative Hodgkin's Disease. *Proc Staff Meet Mayo Clin* 86: 124-128, 1941.

²⁴⁴Brain R. J. Hodgkin's Disease With Dermal and Subdermal Nodules and Purpura. *Brit J Dermat* 42: 445-448, 1930.

²⁴⁵Rullison R. H. Hodgkin's Disease of the Lymphatic System and of the Skin. *Arch Dermat & Syph* 88: 1202-1203, 1937.

Sometimes underlying structures like lymphatic nodes are primarily involved and the skin is invaded later in a scrofuloderma like fashion.^{246, 248}

Specific oral lesions seem to be rare.²⁴¹ Paltauf²⁴² suggested that the lymphatic tissues of Waldeyer's ring were the portal of infection but clinical oral or pharyngeal symptoms are very rare considering the frequency of cervical lymphomas. Only a few cases of ulcerative tonsillitis followed by specific neck nodes have become known.^{430, 431} The rarity of tonsillar lesions compared with the frequency of cervical lymph node involvement does not rule out the tonsils as portals of entry.²⁴¹

Infiltrations and aphthoid lesions of the tongue as well as buccal pigmentations²⁴³ have been seen. In one case the tongue and oral mucosa and the glans penis showed a patchy exfoliation without any other skin manifestations.^{243, 245}

Diagnosis and Histology—The diagnosis of cutaneous lymphogranulomatosis rests mainly on the diagnosis of systemic Hodgkin's disease and on the histological findings in lymph nodes and in the skin lesions. The use of stained lymph node imprints on glass slides for the demonstration of characteristic cells has lately been recommended.⁴¹⁶ The specific lesions consist of foci of dense cellular infiltration in the corium and in the subcutaneous tissues. The infiltrate is made up of lymphoblasts, small lymphocytes, plasma cells, fibroblasts, epithelioids, mast cells and granulocytes. Among the latter eosinophiles are sometimes found in large number. The most characteristic cell of the polymorphous granulation tissue is a large cell with much protoplasm and containing one or several deep staining nuclei. These nuclei are usually large and rich in chromatin and contain nucleoli which stain deeply with eosin. Less often the nuclei are pale (Sternberg after Schoenhof³⁹⁹). These are the so called Sternberg and Dorothy Reed giant cells. They are irregularly scattered throughout the granulation tissue which suggests a process of chronic inflammation rather than neoplasm. However transformation into true sarcoma occurs.

Tappeiner⁴¹¹ emphasizes the almost constant occurrence of lipid filled phagocytes (pseudoxanthoma cells).

²⁴¹ Pick W. Lymph granulom. Zbl 45: 14.

²⁴² Paltauf R. H. Hou t P. L. Flor nlin P. and Louyot P. Observation d'un cas de forme cutanée ulcéreuse d'un lymphogranulomatoses maligne. Bull. et mém. Soc. Méd. hôp. le Paris 49: 1144-1148, 1933.

²⁴³ Searl F. and Liao M. E. Ulcerati Hodgkin's Dis. of the Skin. Arch. Dermat. & Syph. 33: 114-14, 1933.

²⁴⁴ Paltauf R. Über die Eintrittspforte des Virus d. Lymphogranulomatoses. Wien klin. Wchn. 42: 437-439, 1933.

²⁴⁵ Nicolas J. Massin H. and Roussel J. Un cas d'adénite éosinophilique primitive (maladie de Paltauf-Sternberg). Bull. Soc. française de dermat. et syph. 40: 367-37, 1933.

⁴¹² Zoltá G. Eine Riesen-Rachenerkrankung bei Lymphogranulomatosis. Monatschr. f. Ohrenh. 43: 73-74, 1933.

⁴¹³ Bach F. Lymphogranulomatose mit Hautinfiltration. Arch. f. Dermat. u. Syph. 135: 31-36, 1931.

⁴¹⁴ Charlitt H. Hodgkin's Disease confined to the Lymphogranulomatosis Confined to the Oral and Penile Mucosa. Case. Arch. Dermat. & Syph. 24: 244-250, 1931.

small to draw conclusions with regard to an infectious nature. The grouped lesions link with the cases with large tumors in small numbers. A large node or plaque may be surrounded by satellites ¹²²⁻¹²³. Such plaques may reach hand size or may cover half of the scalp or even half of the chest ¹²⁴ or one groin ¹²⁵. These giant plaques are quite suggestive of Hodgkin's disease and are rarely found in other lymphoblastomas. Tumors of the face ¹²⁶ and of the ear lobes ¹²⁷ some times in symmetrical arrangement ¹²⁸ may create *facies leonina*. Local trauma may be followed by development of tumors. The consistency of the tumors



Fig. 313.—Hodgkin's disease. Ulcerated cutaneous tumor of the anterior chest wall.

varies with the depth and the degree of regression and scarring. An uneven firmness is a frequent finding (Wirz after Schoenhof ¹²⁹). The color of these lesions is described as red to dirty yellowish and brown. Most describers emphasize the tendency to ulceration and sinus formation ¹³¹. The whole giant tumor plaque may become an ulcer with undermined ¹³² or infiltrated edges leading to invasion of deeper structures even bones.

¹²²Orehouse C. A. and Corn H. V. H. Lymphoblastoma (Hodgkin's Disease) of the Scalp. Case Arch. Dermat. & Syph. 29: 569-3 1934.

¹²³Kierland H. H. and Montgomery H. Cutaneous Ulcerative Hodgkin's Disease. Proc. Staff Meet. Mayo Clin. 16: 124-5 1911.

¹²⁴Brain H. J. Hodgkin's Disease With Dermal and Subdermal Nodules and Purpura. Brit. J. Dermat. 42: 445-449 1930.

¹²⁵Rullison H. H. Hodgkin's Disease of the Lymphatic System and of the Skin. Arch. Dermat. & Syph. 25: 1202-1203 1937.

nodules in the skin or in the subcutaneous tissue. Their number may be very great.^{2303 2446 448} There is a definite tendency to spontaneous regression which is rarely found in metastases of other malignant tumors. The metastatic nodules are occasionally seen in close proximity to the primarily involved lymph node.²³⁰⁸

Sometimes mediastinal lymphosarcoma penetrates the chest wall and invades the skin. Even such advanced lymphosarcoma may still be clinically curbed by x-ray therapy. The incidence of metastatic nodules in the skin is given as 5 per cent.⁴⁹ and as 13.9 per cent of 122 cases.²³⁸⁰

The diagnosis is usually assured by biopsy. There is profuse proliferation of a single type of cell, invasion of the capsule of the node and the neighboring tissues, abundance of atypical lymphoid cells without notable endothelial and reticulum hyperplasia, and lack of Sternberg-Reed cells.⁴⁹ Differentiation from other lymphoblastomas is not always possible.²⁴⁴⁸ The therapy is radiological and surgical.

²⁴⁶Riehl ■ Jr. Hauterscheinungen bei akuteukämischer in Lymphosarkomatose Übergangend zu Lymphadenos. Arch f Dermat & Syph 169 900 11 1933

²⁴⁷Rieser Fall zur Diagnose. Zbl 45 11

²⁴⁸Finsen Lymphosarkomatois Cutis. Zbl 39 619

²⁴⁹Cohn S and Riehl r M. Modern Views on Hodgkin's Disease. M Rec 148 243 1938

CHAPTER XXXIII

DISORDERS OF THE BLOOD AND THE BLOOD FORMING ORGANS

Anemia ⁴³⁰ 431

The red blood cells are formed from endothelium in the red bone marrow. They pass through various stages of development (megakaryoblast, normoblast, reticulocyte) before they are released into the blood stream. Besides the material necessary for the development of all cells, two specific substances are required for the normal development of erythrocytes: iron for the formation of hemoglobin and the erythrocyte maturing factor (E.M.F.) which is produced in the gastric mucosa and stored mainly in the liver. After a life span of from two to six weeks, the red cells die and their remnants are phagocytized by the reticulo-endothelial cells in the spleen. Eighty-five per cent of the iron is used again, and bilirubin, the other end product, is under normal conditions excreted by the liver.

The function of the red cells is the transport of oxygen from the lungs to the tissues. Anemia is a reduction below normal of the capacity of the blood to transport oxygen. ⁴³² It may result from too small numbers of functioning red cells or from deficiency in their function, due especially to lack of hemoglobin. The clinical forms and stages of anemia are mostly explained by the phase in which a damaging influence hits the growing or mature red cell. For example, in the case of anemia from massive hemorrhage the mature cells are reduced in number. In the case of pernicious anemia the maturing of the red cells within the bone marrow is disturbed by a deficiency of the E.M.F. and so they die to a large extent in the bone marrow, only an insufficient number of immature cells being released. The bilirubin left over from the hemoglobin of the masses of dead red cells increases the bile pigment in the blood and may cause icterus.

Dermadromes — *Pallor* is seen in practically all anemias and is directly proportional to the loss of hemoglobin. ⁴⁴³

In *hypochromic anemia* (chlorosis), which is rare today, the pallor sometimes takes on a slightly greenish tinge. Capillaroscopy shows the capillaries in various types of severe anemia to be pale, thin, or even empty, and filament like with the arterial and venous sections hardly discernible.

The estimation of pallor from the face and the mucosae is often deceiving. Duke advises a quick test: compare the palms of the patient with those of a normal person. The palms should be held at heart level. The advantage of the test which supposedly is quite accurate, is the independence of the palms to emotional erythema and light.

⁴⁴³ Meutengracht, E. Some Etiological Factors in Pernicious Anemia. A Symposium on the Blood and Blood Forming Organs. Madison, Wis. 1939, the University of Wisconsin Press.

Chevallier⁴¹ enumerates the following dermatoses as occasionally seen in essential anemias: Rhagades of the fingertips and lips, smooth atrophic tongue and buccal mucosa, pruritus vulvae, precocious graying of the hair and intertriginous erythema. Corroboration of these impressions is still lacking although a similar list which includes onychomycosis is given by Simon.⁴²

Pernicious Anemia

Besides the pallor found in other anemias too a yellowish discoloration is characteristic of this disease. It is caused by the increased content of bilirubin from prematurely destroyed red cells and to a lesser extent from other substances in the blood plasma. The icteric index may be above ten normal is four to six. The third factor which influences the color in pernicious anemia is pigmentation which though rarely may reach degrees which suggest Addison's disease. The pigmentation is mostly described as diffuse; sometimes it has a predilection for the trunk, chest, abdomen and the dorsa of the hands. As in Addison's disease the creases, folds or scars may be darker than the surrounding skin.⁴³ Freckled or lentigo like spots have been seen within the diffuse melanoderma (Lennartz after Kaufmann⁴⁴). Another similarity to Addison's disease is found in slate colored or brownish spots on the oral mucosa. Not only may the symptoms of Addison's disease occur in pernicious anemia but even post mortem findings of adrenal atrophy are on record.⁴⁵ Bogorad⁴⁶ saw improvement of the pigmentation under cortin while liver therapy alone failed to change it. Most authors suggest that the melanosis in pernicious anemia is a hemosiderosis derived from the blood but the histological evidence is scanty and not clear.^{46, 46a} The possibility of arsenical melanosis must be considered since arsenic was and still is used in pernicious anemia. Patients with pernicious anemia under treatment with liver extract are supposed to tan more readily than normal persons.⁴⁷ In a very extensive case of cutaneous and mucosal pigmentation in pernicious anemia the author could not notice any effect of liver therapy on the pigmentation despite good response of all other symptoms. Ulcers of the lower legs which are more often seen in other forms of severe anemia are very rare in pernicious anemia.⁴⁸

The symptom known as *Moller's or Hunter's glossitis* is of practical importance because it may precede all other complaints and the hematological findings

⁴¹Chevallier P: Die Dermatosen der Anämie Med Welt 10: 1201-2: 1936

⁴²Simon C: Anémie etc. Paris méd 1: 47-51: 1939

⁴³Bogorad A G: Hyperpigmentation of Skin in Bile mercuric Anemia. Brit med 18: 94-95: 1940
Zbl 28: 104

⁴⁴dequerra J H and Patton I V: Case of Erythoderma With Lymphocytosis Brit J Dermat 32: 378: 1941

⁴⁵Gantenberg R: Hautpigmentation und Hautreaktion bei perniziöser Anämie Deutsche med Wchnschr 67: 1574: 1941

⁴⁶Churany T: Pigmentierungen der Haut bei perniziöser Anämie Arch f Dermat u Syph 121: 746-761: 1936

⁴⁷Lasch F: Blingeschwüre bei perniziöser Anämie Deutsche med Wchnschr 65: 377-378: 1939

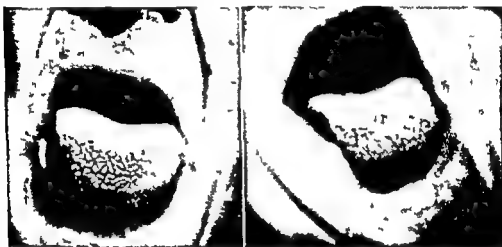
PLATE V

- 1 Pellagra - Erythema of dorsum manus (Courtesy Wisconsin General Hospital)
- 2 Scurvy - Gingivitis (Courtesy Wisconsin General Hospital)
- 3 Ecchymoses in acute lymphatic leukemia (Patient of Dr. E. Kay)
- 4 Pernicious anemia untreated - Acute glossitis involving mainly the edges - Filiform papillae are still present - Note ecchymosis
- 5 Pernicious anemia - Pale slick tongue - Atrophy of papillae
- 6 Erythema nodosum



PLATE V

in pernicious anemia ^{453 460} The condition starts with a burning sensation in the tongue and occasionally in other parts of the mouth The pain and sensitivity to acid hard food and smoking often comes in spells Sometimes articulation is hampered In some cases only burning is noticed and no visible changes develop but more often fiery red painful round or oblong erosions appear usually on the dorsum close to the tip The filiform papillae within the patches are at first swollen but soon thinned or absent the fungiform papillae are often swollen and red ^{461 461} The tip and the edges occasionally also the adjacent parts of the dorsum of the tongue are involved but sometimes also the inside of the lips



A

B

Fig. 320 — A Pernicious anemia Subchronic changes The papillae filiformes have mostly disappeared B Pernicious anemia Atrophy of papillae

cheeks and the palate (Harris after O H Foerster ⁴⁶) From the distribution on the tongue a V or U shaped figure results with the opening directed toward the base of the tongue Many authors ⁴⁶⁷ emphasize the contrast of the fiery red lesions on the tongue to the pallor of the other parts of the oral mucosa while others say that the red areas are the healthy ones and the pale areas the changed ones ⁴⁶⁸ These may represent later stages of development The initial erosion is later followed by atrophy of the papillae which results in a smooth surface In extreme cases the atrophy may involve the posterior part of the tongue and the

⁴⁵³Magr W Zur I a. distik d r Glossitis bei perniziö r Anämie Monatsschr F Ohrenh 68 315-318 1932

⁴⁵⁴Heyn W Möllsche Glossitis Hunter'sche Zunge und perniziöse Anämie Dermat Ztschr 47 132 1906

⁴⁵⁵Haselkuss A Möll'sche Glossitis Die B rlin 1931 Zbl 28 783

⁴⁵⁶Hunter W Severe Anemias Their Infective Nature Diagnosis and Treatment London 1909

⁴⁵⁷Foerster O H Dermatoses and Associated Diseases of the Mucosa J A M A 73 653 1919

⁴⁵⁸Zisser E Hautkrankheiten und Mundkrankheiten Möll'sche (Hunter'sche) Glossitis Handb d H u Ok 16 1 111 1930

papillae villatæ. Slight edema of the tongue with visible impressions of the teeth has often been noticed in the early stages (Hunter's³⁴⁴ hacked edges.)

Though most frequently seen in pernicious anemia Moller Hunter's glossitis or similar conditions occur in other severe anemias (tropical and nontropical sprue pellagra alcoholism tapeworm etc)³⁴⁵ The painful red erosions of Moller Hunter's glossitis should not be confused with the dry round sharply outlined plaques fruchées which are seen in syphilis or with the harmless plaques lisses which consist of non-inflammatory round areas which are devoid of papillæ. These completely painless lesions are usually accidental findings. The transitory character and the fast traveling over the dorsum within a few days are characteristic of the wandering rash of the tongue. The restriction of a chronic inflammation to a diamond shaped area in the center of the posterior tongue marks the rhombic median glossitis.³⁴⁶ Liver therapy relieves the glossitis in pernicious anemia and so it has become rather rare. If the patient sticks his tongue out anemic stripes appear which correspond to the contracted muscles (Arndt after Heyn³⁴⁷). This sign is considered valuable in early diagnosis. The tongue is hardly ever coated.

Sickle Cell Anemia

This is a severe hereditary anemia which derives its name from the characteristic sickle or spindle shaped erythrocytes (drepanocytes) which occur in great numbers as do other bizarre forms of the red cells. The disease has almost exclusively been seen in Negroes in a few instances in Sicilians.³⁴⁸ Jaundice is almost always noticeable.³⁴⁷

Dermadromes—Punched out sometimes serpiginous unilateral or bilateral extremely chronic ulcers near the ankles are common in this anemia. They were seen in twenty out of twenty eight cases³⁴⁹ and in 55 out of 214 cases.³⁴⁷ These ulcers often develop after minor injuries. Poor circulation in the lower legs and the known tendency to thrombosis in sickle cell anemia probably are pathogenetic factors. Priapism which has repeatedly been seen in sickle cell anemia also can be explained by thrombosis in the vascular system of the penis.³⁴⁹

Therapy of the ulcers should consist of nonirritating local medication and treatment of the underlying anemia.

Similar leg ulcers have been seen in a considerable number of cases of *hemolytic anemia* (hemolytic jaundice). This is a hereditary anemia characterized by unusual spheroid shape of the erythrocytes. These ulcers sometimes only heal

³⁴⁴Man on Bahr P. H.: *Glossitis and Vitamin B Complex Deficiency in England and Allied States* Lancet 2: 317-356 1940.

³⁴⁵Boeck and Jørgensen: *Chloroform and the tongue* Medd. Nord. Med. Selsk. 1914 1915.

³⁴⁶Greenwald L. and Hurrett J. B.: *Sickle Cell Anemia in White Family* Am. J. Med. Sc. 1939 764-774 1940.

³⁴⁷McCarty K. T. B. and Nussbaum C. C.: *Skin Manifestations of Sickle Cell Anemia* Urol. & Cutan. Rev. 46: 194-200 1941.

³⁴⁸Cummis C. L. and LaRocca C. G.: *Ulcers of Legs in Sickle Cell Anemia* Arch. Dermat. & Syph. 42: 1015-1039 1940.

³⁴⁹Getzoff P. I.: *Priapism and Sickle Cell Anemia* J. Urol. 48: 407-411 1942.

after splenectomy.⁴⁷⁰⁻⁴⁷⁴ The jaundice in hemolytic anemia supposedly does not itch as other types of icterus usually do.⁴⁷⁵



Fig. 3-1.—Female aged 18 years. Sickle cell anemia. Leg ulcer. (From McGavack, T. H. *Urol. & Cutan. Rev.* 1941.)

⁴⁷⁷ Taylor, E. S. Chronic Ulcer of the Leg Associated With Congenital Hemolytic Jaundice. *J. A. M. A.* 112: 1574, 1939.

⁴⁷⁸ E. tape, J. d. A. Ulcus cruris y esplenectomia n. t. r. e. e. n. m. o. l. i. t. i. c. a. R. v. d. c. i. r. B. r. e. e. l. o. n. a. 1: 447-459, 1931.

⁴⁷⁹ Lau, H. J. Unterschenkelgeschwür bei hämolytisch m. Ikterus. *Klin. Wchnschr.* 10: 409, 410, 1931.

⁴⁸⁰ Joppe, F. H. Schwere bilbare Fußgeschwüre bei hämolytisch m. Ikterus. *Klin. Wchnschr.* 9: 10-1, 1930.

⁴⁸¹ Joppe, F. Ein Fall von Ikterus hämolyticus mit Unterschenkelgeschwüren. *Milz. Atropa. tion Norsk. mag. f. læg. v. i. s. k.* 25: 63-71, 1934. III: 60, 2.

Hypochromic Anemia, Plummer-Vinson Syndrome—Dysphagia an atrophic oral mucosa anemia and often spoon nails or thin nails constitute a syndrome which does not seem to be rare. Described by Vinson²⁴⁷⁵ in 1922 as hysteric dysphagia but observed before it has been confirmed by reports from many countries.²⁴⁷⁶ It seems to occur more frequently in Sweden than in other countries.²⁴⁷⁷ The patients are almost exclusively women mostly in middle age. Idiopathic hypochromic anemia with pallor but without jaundice is the most



Fig 392.—Female aged 18 years. 9 years of achlorhydria. Hemoglobin 49 per cent. Hb C 166 million. Hemolytic icterus. Amenorrhea. Ulcer of the lower lip exists for two years without any response to treatment. It developed after a dog bite. (From McCave & T. H. Urol & Cutan Rev 1941)

constant feature of the syndrome.²⁴⁷⁷ The red cells usually do not fall below 4 000 000 but the hemoglobin is reduced to 50 per cent or less. Achlorhydria is seen in 75 to 90 per cent of the cases and moderate splenomegaly in

²⁴⁷⁵Vinson P. P. Hysterical Dysphagia. Minnesota Med 5 107 19

²⁴⁷⁶Ahlborn H. E. Achlorhydric Anemia. Plummer-Vinson Syndrome and Carcinoma of the Mouth Pharynx Esophagus in Women. Brit M J 2 331 333 1936

²⁴⁷⁷Anderson N. P. Spoon Nail Anemia Chelitis and Dysphagia. Arch Dermat & Syph 27 816 822 1938

25 per cent. Complaints of burning tongue especially after eating fruit and other acid food often lead the attention to the changes in the mucosa of the upper part of the gastrointestinal tract. The patients have great difficulty in swallowing solid food so that their mealtime is prolonged.

They soon arrive at a liquid or semiliquid often deficient diet.

Dermadromes and Oral Manifestations—There is cheilitis varying from minor fissures to hypertrophic chronic inflammation or perleche. Buccal leukoplakia occurs. After a time the lips become thin and the mouth shrinks. Ahlborn²⁴⁵ who has given a very detailed description believes that the shrinking of the lips is part of the same atrophic process which leads to the changes in the tongue and esophagus. Possibly the fact that these patients often lose their teeth early has some significance. The surface of the tongue is described as glazed red dry smooth and devoid of papillae.^{247 478}

There is much similarity to Hunter's glossitis but the involvement of the mucosa seems more widespread and more constant. It not only involves the mouth but it extends to the upper—rarely the lower³⁰—part of the esophagus. Spastic or cicatricial stenosis of the mouth of the esophagus web formation across the lumen ulceration and other symptoms have been seen.^{478 2479} Cancer of the esophagus and multiple oral malignancies have been observed. Especially in the relatively rare instances of cancer of the lip in women should the thought of anemia and Plummer Vinson's syndrome enter the mind.^{2478 477 2479} The post cricoid cancer of the esophagus which in 70 per cent to 90 per cent is encountered in women probably belongs here.⁴⁷⁶ Association of Plummer Vinson syndrome and kraurosis vulvae is also known (Rhoads after P. Gross²²⁴⁷).

Only recently after many cases of Plummer Vinson's syndrome have been described without mentioning koilonychia have spoon nails been discovered to form a rather frequent (about 70 per cent) dermatome in hypochromic anemia.^{2307 478 47} The free edge of the nail is thin and sharp as if gnawed on. The nail breaks or splits easily and in less complete cases the nail is only flat and thin. It should not be forgotten that koilonychia may be produced by occupational factors e.g. work in soap suds and oils. Dry gray pepper and salt hair are also mentioned in case reports.⁴⁶⁰ The similarity of Plummer Vinson's syndrome with ariboflavinosis has been emphasized.²⁴⁸²

The treatment of the syndrome consists of administration of iron in liquid form hydrochloric acid riboflavin²⁴⁸² and bougieing of the upper esophagus which seems to be particularly helpful in relieving the dysphagia and facilitating a proper diet. The oral as well as the nail changes are capable of complete restoration.

- ²⁴⁷⁸ K. A. J. D. Plummer Vinson Syndrome 2 Cases Arch Otolaryng 82 66-67 1940
²⁴⁷⁹ G. Klinge P. G. Disorders of Mouth of Esophagus in Syndrome of Plummer Vinson (Dysphagia With Anemia J. Laryng & Otol 53 143-153 1940
²⁴⁸⁰ Damesh K. W. Primary Hypochromic Anemia J. A. M. A 100 540 1933
²⁴⁸¹ Meuleman G. and Dick J. J. Riboflavin A. Hemostasis and Plummer Vinson Syndrome Klin. Wchnschr 20 831-833 1941

Cranulopenia (Agranulocytosis)

Granulopenia¹⁰⁷ ¹⁰⁸ ¹⁰⁹ is a deficiency of the blood in granulocytes caused by failure of the bone marrow to produce or release these cells. It may be caused by toxic and allergic reactions¹¹⁰ to drugs such as arsphenamine, trinitrophenol, benzol, amidopyrine, sulfonamides and gold, by radiant energy, by infection, and by allergic reaction¹¹¹. Cranulopenia also occurs secondarily to hyperplastic processes in pernicious anemia or leukemia. Low leukocyte count—sometimes as low as fifty—acute sore throat, exhaustion, severe malaise, fever, and a moderate degree of icterus are in 50 per cent of the cases the manifestations of this dangerous disease. The spleen is often enlarged. Cases without any mucosal symptoms occur.¹¹² The red cell and platelet counts are essentially unaltered; this accounts for the usual lack of hemorrhagic symptoms.¹¹³ ¹¹⁴ ¹¹⁵ If they too are deficient (pan myelophthisis) hemorrhages occur.¹¹⁶ The resistance to infections is extremely low. The mortality in untreated cases was seventy-eight per cent in a large series. Death may occur within thirty-six hours from the apparent onset.¹¹⁷



Fig. 323.—Agranulocytosis. Fehrmann's phenomenon.

- ¹⁰⁷Hunter R. J. Agranulocytic Angina. *Med. Clin. North Am.* 1: 11 1669 1931 1933.
¹⁰⁸Marin A. La granulopélie maligne. *Union Méd. du Canada* 11: 126 2 359 469 1940.
¹⁰⁹Madiou E. V. and Souli T. L. Agranulocytosis. *J. A. M. A.* 102 755 759 1934.
¹¹⁰Clemens G. Granulocytopenia in Lupus Erythematosus. *Internat. Congr. Med. Res.* 109 1310 1313 1939.
¹¹¹Jackson H. Jr. and Tighe T. J. C. Treatment and Mortality of 390 Cases of Acute Agranulocytosis. *New England J. Med.* 220 729 733 1939.
¹¹²Plum I. Clinical and Experimental Investigations in Agranulocytosis. *Lancet* 1937 II 11.
¹¹³Lewis C. Ltd. and Copehagen 1937. *Nyt Nordisk Forlag* Arnold Busck.
¹¹⁴Stashlin R. Agranulocytosis and Leukemia. *Internat. Congr. Med. Res.* 1419 14 3 1938.

Oral Manifestation and Dermadromes—Angina is so much a part of the syndrome that the disease is often referred to as agranulocytic angina. Bucco-pharyngeal lesions are seen in 84 per cent.¹⁰³ The soft palate, uvula and anterior



Fig. 3-4—Agranulocytosis. Ecchymoses. (Courtesy Dr. Frick, Chicago.)



Fig. 5—Agranulocytosis. Cheilitis and gingivitis. Patient also had angina.

pillars are red and eroded, the redness being sharply bordered against the normal mucosa.¹¹⁵ The tonsils are enlarged and red, sometimes with small white specks, sometimes with severe ulcerations. Ulcerations in other parts of the oral cavity and also in the nose¹¹⁶ have been observed, sometimes without involvement of

¹⁰³R. H. A. (Agranulocytosis) With Peculiar Changes in Nasal Mucosa. *Monatschr. f. Ohrenh.* 74: 630-637, 1940.

the tonsils³¹⁰ Gingivitis with adherent foul smelling pseudomembranes³¹¹ is often present The gums bleed easily Rarely the ulcerations invade the bone or spread to the deeper tissues of the pharynx and larynx Edema of the glottis may necessitate tracheotomy³¹² ³¹³ ³¹⁴ Fusiform bacilli and large spirilla are commonly found The cervical lymph nodes are swollen but there is no generalized adenopathy



Fig 36 - Agranulocytosis due to diethylphenol poisoning (Courtesy Dr Arthur Linker)

The face is often cyanotic sometimes pallid or congested⁴⁹⁷

Cutaneous ulcerations about the body openings mainly around the mouth and nose were described by Landsberg⁴⁹⁸ The necrotic lesions are mostly small⁴⁹⁹ but severe edema and lymphangitis may be present so that anthrax or other infections are simulated Cellulitis and deep noma like destructions are rare events Ulcerations in the neighborhood of the anus⁵⁰⁰ or the genitalia⁴⁹⁷ have been observed quite frequently²¹³² ⁴⁹⁹ ⁵⁰⁰ Exanthems of erythematous pemphigoid vesicular papular or hemorrhagic⁵⁰¹ character and occasionally

³¹⁰ Bellard M and L.bourg L. "Syndrome agranulocyttaire à défaut buccal" Cufrison de l'ulcération buccale Evolution vers un syndrome au leucémique avec anémie pernielle Rev de stomatol 38 621-627 1933 Zbl 47 584

³¹¹ Dahmen Agranulocytosis Zbl 48 354

Kruspe Die Dahmen Zbl 41 559

³¹² Lothoven W J. Bilateral Larynx krose bei Agranulocytose Arch f Ohrenh 147 190 1930 1940

³¹³ Helmsmoortel J Jr and Mulders M. Agranulocytosis With Buccopharyngeal Infection 2 Cases Ann otol laryng pp 231 87 1940

³¹⁴ Landsberg M. Hautveränderungen bei Agranulocytose Mel Klin 26 19 1933 1930

⁴⁹⁸ Buck H W. Agranulocytosis With Anal Ulcer JAMA 146 1463 19 11

⁴⁹⁹ Reye E. Ueber Haut und Schleimhautveränderungen bei der Agranulocytose Dermat Wehnschr 89 1895 1899 9

⁵⁰⁰ Portier L. Agranulocytose nécrose cutanée Union méd du Canada 41 240 1935

⁵⁰¹ Greenbaum S S. Acute Cutaneous Infection Associated With Agranulocytosis or Agranulocytosis Arch Dermat & Syph 28 135 136 1933

⁵⁰² Dalous and Fabre J. Les lésions cutanées de l'agranulocytose Arch d mal du coeur 27 645-656 1934

⁵⁰³ Allan W. Agranulocytic Angina With Thrombopenic Purpura Ann Int Med 2 51 544 1928

typical erythema exsudativum multiforme have been recorded⁴⁸ 487 500 1 503 Marin⁴⁸³ has seen giant herpes of the lips Pentnucleotide in large doses a stimulant for the production of leukocytes is considered helpful by many authors Otherwise the therapy is symptomatic Recently pyridoxin by intravenous injection has been recommended⁴⁹

Polycythemia⁵⁰

Compensatory increase of the erythrocytes (above 6 000 000 in men and above 5 500 000 in women) occurs under various suboxemic conditions e.g. low barometric pressures carbon monoxide poisoning and certain types of heart disease Such secondary increases of the red cells hardly ever exceed 8 000 000 Polycythemia vera is a disease of the bone marrow In this condition much higher sometimes enormous increases of the blood volume and of the red cells per cubic millimeter of blood occur The viscosity of the highly corpuscular blood of course is high After an asymptomatic phase which may last years cyanosis dizziness headache and quite often hepato splenomegaly develop Bleeding occurs from the nose and gums due to congestion rather than to a hemorrhagic tendency Variations of the normal syndrome include combinations of hypertension and especially in the final stages leukemia and anemia⁵¹

Dermadromes—The most common and at the same time most striking dermadrome of marked polycythemia is the *redness of the skin* This discoloration is most marked on the hands and face although in some cases it may be noticed over the entire body surface The shade and intensity of the erythema varies from a dusky purple cyanosis to a deep or in spots bright red Red as a rose in summer and blue as indigo in winter is descriptive of the changes under the influence of weather and temperature Oskar⁵⁰⁸ who used this description said that one of his patients was jokingly called the blue baby There is erythema in areas which usually do not take part in other erythemas e.g. the temples and the skin under the ears and between eye and nose The redness of the conjunctivae creates an impression of rage Contrary to congestion from other causes the redness stays constant during rest and sleep⁵¹⁷ While the erythema seems to be fairly even one can on close inspection and under glass pressure detect telangiectases on the red background This is particularly true of the mouth Capillaroscopy shows that the capillaries are dilated it is here and in the spleen where much of the excess blood is bottled up⁵¹⁸ Superficial telangiectases in the face often give the patient a ruddy complexion Besides

⁵⁰ Corti E Ag anuloct Ned r l t l l chr g esk p 37 1 1934 Zbl 61 52

⁵¹ Ellman P and Law J S Agr auto yto is With Pu pura Hemorrhagica Following Cold The spy l r ntion of Complications Brit M J 2 1 6 3 1937

⁵² Kn t m Tr tment of Leukop nia and Cr polocytop nia With Pyridoxin Acta Med Scand 125 3 6 1940

⁵³ Rosenthal N and Bas P A Poly yth mi Course Arch Int M d 62 803 917 1938

⁵⁴ O l W Chroni Cyano i With Poly yth mia a d Enlarged Spleen N w Clin l al Pntty M Class 1 4 1 7 1939

⁵⁵ D eek G at i D ekhorn E Poly ythe ia Med J lin 25 III 4 16 6 1939

⁵⁶ Bonn C F a i h a d Ch Mea urum t o tl Skin Capillari n Ca es of Poly yth mia Ver Role of the Capillaries i th l eduction f F ythrost J Clin Investigation 2 4 3 19 6

linear telangiectases small deep cherry red papular hemangiomas are known to occur in polycythemia

The color of the oral mucosa is deep cherry red. Relatively early in the course of the disease the soft palate may appear considerably redder than the hard palate so that the borderline is marked.¹¹⁷ In the cyanotic stage the tongue is swollen deep purple and the papillae atrophic. Bleeding from the blood gorged gums occurs but is slight since there is no hemorrhagic tendency.^{210 211}

Small pigmented spots are often scattered over the reddened areas. They are probably due to hemosiderin deposits after small hemorrhages.

Telangiectases and petechiae constitute the elements of *purpura annularis telangiectodes*, a dermatosis which has been found to be a dermatome of a considerable number of milder cases of polycythemia.^{112 113} Without preceding hyperemia or infiltration small lavender to purple colored spots appear. These maculae consist of capillaries and petechiae. The lesions appear in crops. They often start in a follicle and spread peripherally leaving a slightly atrophic scar and resulting in rings¹¹⁴ and polycyclic figures.

The tourniquet test is usually negative.

The viscosity of the blood, the high platelet content, the large blood volume and the high blood pressure favor a variety of vascular disturbances.

Thrombosis has been observed in many organs and is together with arteritis responsible for gangrene ranging in severity from the blistering of a toe to the loss of an extremity.^{211 212} Various ulcerations of the lower legs have been observed.^{213 214} Circulatory disturbances account also for the many instances of paresthesias. Raynaud like symptoms and transitory painful red warm areas similar to erythromelalgia^{211 212 215} Norman and Allen²¹⁶ reporting on ninety eight cases of polycythemia mention arterial disease in 33 per cent.

Rosacea in polycythemia has been described several times although some of the cases had better be grouped with *acne urticata*, a relatively rare dermatome of polycythemia. *Acne urticata* is a chronic itching dermatosis which resembles prurigo quite closely. It starts on the face but has a tendency to involve the back and the extensor surfaces. It develops from an urticarial papule with a

Kupfman B J Symptomatology of Erythremia *Vestn Otol i t d* 2 210 215 1937 Zbl 87 466

Sautej M Skin Changes and Pathogenesis of Vaguer Disease *Venerologia i Dermatologia* pp 714 755 1926 Zbl 23 672

Sauter J v Skin Changes in Erythremia Zbl 26 37 1929

Gottlieb H Purpura Majocchi A ch f Dermat u Syph 189 355 1929

Hiruna r St Purpura annularis telangiectodes Majocchi Zbl 28 587 1931

Wilmanns H Hauterkrankungen bei Polycythemia vera Dtsch Med Wochenschr 1937

Herrick R F Pathological Features of Polycythemia vera J Clin W Pathol 11 1260 1937

Tubin M Trophoneurotic changes in Erythremia Zbl 25 766

Zitter W J Peripheral Vascular Disturbances in Polycythemia N Clin North Am Lea 21 485-492 1940

Hallam J Ulcerated Nodules on Legs Associated With Splenomegalic Polycythemia Br J Dermatol 42 97 1930

Gräfe v P Ein Fall einer kombinierten Erythromelalgie und Polycythämie Russk Klin 11 35 19 9 Zbl 11 8

Gans M Polycythemia vera Vichows Arch f path Anat 263 565-573 1937 Zbl 11 62

Norman I L and Allen E V Vascular Complications of Polycythemia Am Heart J 257 274 1937

central vesicle which soon becomes excoriated. The crust covered lesion may ulcerate and heal with a pigmented scar. Crops of new lesions follow each other. The condition has much similarity to prurigo lymphatica which occurs in leukemia. Thus acne urticata represents another link to leukemia which not infrequently constitutes the final stage of polycythemia.⁵

The treatment of polycythemia is to remove or destroy the excess of erythrocytes by blood letting, irradiation, phenylhydrazine, arsenic and other drugs.

⁵⁵ Weldman F. B. and Klauder J. V. Acne Urticata Polcythaemica. Positive Oxydase Reaction in Lesions Macroscopically and Microscopically. Arch. Dermat. & Syph. **39**: 645-668, 1939.

CHAPTER XXXIV

DISORDERS OF THE BLOOD AND THE BLOOD FORMING ORGANS

Hemorrhagic Diseases

The characteristic common to all diseases of the hemorrhagic group is abnormal bleeding. The flow of blood from an injured vessel starts a sequence of mechanisms. The injured small blood vessel contracts slowing down or stopping the bleeding. Macleod² explains this primary vascular constriction by assuming that the flow of blood removes the distorting histamin like substance released by trauma. Blood platelets then form a clot which is finally reinforced by the formation of fibrin. The vasoconstriction is a quick response which slows the flow of blood sufficiently so that the platelets can collect from the blood and form an adherent thrombus. This clot retracts and closes the wound firmly and permanently. Since the contracted vessels relax after a certain period of time blood would start flowing again and the clot would be pressed out if it had not become firmly adherent and by its power of retraction pulled the walls of the injured vessel together.³ This mechanism of hemostasis may be disturbed in any of its phases. There may be lack of capillary reaction clotting may fail or a combination of both may occur. Abnormal bleeding will result in any case. Furthermore decreased resistance of the capillary wall is an important factor in many hemorrhagic diseases.

In thrombocytopenic purpura lack of capillary contractility and a low platelet count are combined. The bleeding time is prolonged just as it is in athrombocytopenic purpura where the platelet count is normal. In Osler's disease the trouble is completely vascular and restricted to the capillaries. In hemophilia fibrinopenia pseudohemophilia purpura and hemorrhagic disease of the newborn defective coagulation is responsible in the two latter conditions being combined with capillary dysfunction.⁴

Capillary capillary observations⁵ suggest that the blood of ecchymoses does not come from the capillaries but from the subcapillary venous plexus. Fresh petechiae have a red color. This is probably due to the presence of engorged very superficial small vessels and a small amount of extravasated blood in the upper layers of the cutis. The combination of vasodilatation and free hemorrhage in the deeper layers produces a bluish lesion.⁶

Blood Coagulation - The transformation of fibrinogen a labile colloidal blood protein which is probably formed in the liver or perhaps in the reticulo

² Macleod J. G. Mechanism of Hemostasis Quoted J. Med 10 1 29 1941

³ J. G. Macleod. Capillary Mechanisms of Hemostasis. Blutstillung und Blutparasiten. D. Deutsches Arch. f. klin. Med. 175 534 14 1933 Zbl. 47 479

⁴ Leick G. M. Rosenthal N. and Frick L. Purpura. Classification and Treatment With Special Reference to Factor VIII Deficiency. Arch. Dermat. & Syph. 35 831 867 1937

endothelial system into fibrin of which the clot mainly consists is only the final phase of the chain of reactions which constitute coagulation. The formation of fibrin from fibrinogen needs an enzyme thrombin which is not present in the circulating blood since the blood would otherwise coagulate in the vessels. If needed it is synthesized from a liver protein called prothrombin and free calcium ions. Naturally the prothrombin too must be held inactive under normal conditions. The activator of the prothrombin is thromboplastin which is held ready in the blood platelets.

The most important methods used to diagnose a hemorrhagic disease are ⁸⁸⁰⁻⁹⁰²

1 The *coagulation time* of the blood. Normal blood coagulates in a test tube in one to five to eight minutes (Lee and White)

2 The *bleeding time*. The skin bleeds from a small cut into the ear lobe for from one to three minutes. The bleeding is recorded by blotting on white blotter every thirty seconds (Duke's method). This demonstrates the capillary reaction to injury.

3 The *capillary resistance*. This is most readily tested by the *tourniquet test* (Leede Rumpel test). Haden ⁸⁸⁰ calls the test positive if after placing a blood pressure cuff on the upper arm for three minutes at a pressure of 100 mm. of Hg a crop of petechiae appears below and under the cuff. According to Quick ⁸⁹⁰ the pressure should be kept for eight minutes midway between the diastolic and systolic pressures. The petechiae which are visible to the naked eye within a circle 5 cm. in diameter drawn on the flexor surface of the forearm with the center 4 cm. below the bend of the elbow are counted after fifteen minutes. The test is considered positive if more than ten petechiae appear. Other tests for capillary fragility based on pinching ⁸⁸²⁻⁷ suction ¹⁴⁷⁻²⁵⁻⁶⁻²⁵³⁰ or perfrigeration with ethyl chloride ¹⁰¹ have not become as widely used as the simple tourniquet test. Madison and Squier ⁸⁸ and many other investigators consider a positive Leede Rumpel test a pathological finding of significance. These authors found the test positive in scurvy, severe infections, malignant hypertension, ovarian dysfunction, allergic reactions in the final phase of some malignancies and especially in primary blood diseases. Intradermal injection of 0.1 or 0.2 c.c. of a 1:3000 solution of dried moccasin venom is another method for gauging the capillary resistance ²⁵¹⁵. The test is positive when a hemorrhage of 1 cm. or more in diameter appears within one hour at the site of injection.

⁸⁸⁰Kosch wnikow H W Z Frage d B Schigkeit der Blutg fass d r H ut Arch f B rmat u Syph 187 448-460 1933

⁸⁸²Hamm F Hämorrhagisch Krankh iten Handb d Haut u Gk 6 2 512 III 1929

¹⁴⁷⁻²⁵⁻⁶⁻²⁵³⁰on Ho bely F Leber die Blutungs eitschaft de Haut Mün hen med. Wchnchr 77 846-848 1930

¹⁰¹rom y r E Allg m f e D rmatologi oder Pathologie der Hautkrankheiten Berlin 14.06 G brü r Ho ntraeg r

⁸⁸Cutt J H and Johnson C H Capilla y Fragility A Device for th uly of Capillary H morrhage J A M A 108 505 1935

²⁵¹⁵Frangilla A N w sign of Capilla y Fragility Ell ited ty Ethyl Chlorid Terfrig ratio Ls in Case of O thostatic Pu pura Riv di clin med 41 763-771 1940 Zbl 20 518

⁸⁸Ala lison F W and Squier T L Bleedi g d e to Capillary Defect Wisconsin M J 39 31-34 1940

4 *Clot retraction time* The clot normally separates from the serum in thirty to sixty minutes. If the platelet count is lower than 70 000 no or in complete clot retraction occurs.

5 *The platelet count* The normal platelet count is 250 500 000.

These relatively simple tests are sufficient for the vast majority of cases. For chemical assays of blood components which participate in the process of coagulation see Quick.²⁹⁰

Hemophilia

Hemophilia is a hereditary constitutional lifelong disease characterized by severe bleeding on relatively slight trauma. It becomes manifest only in the male although the daughters of a patient are able to transmit the disorder to their sons. Besides dangerous and often fatal hemorrhages following injuries hemorrhages into body cavities especially joints are common while spontaneous hemorrhages into and from the mucous membranes do not belong to the typical syndrome. Lasting deformities from hemarthrosis are usually present after the age of ten.²⁴²

The typical laboratory findings in hemophilia are prolonged coagulation time sometimes of more than 48 hours while the platelet count the clot retraction and the bleeding time (from puncture or small incision) are mostly normal. It seems contradictory that the bleeding time from small cuts is normal according to most authors and that at the same time the blood needs so much time to coagulate. This is explainable by the intact capillary constriction and by the fact that hemophilic blood still clots a little when passing over hemophilic tissue.^{290-292 293}

The presently accepted explanation for the pathogenesis of hemophilia is the resistance of the platelets to disintegrate and to release the thromboplastin. This in turn prevents the release of the prothrombin which is needed for clotting. Why the blood platelets are so resistant is unexplained.²⁹⁰ A vascular factor consisting of pathological vasodilatation on slight stimuli (Ricker after Gottron²⁴²) may play a part.

Dermadromes—In contrast to other hemorrhagic diseases hemorrhagic skin lesions are not a dominant feature. There are usually no petechiae and the tourniquet test is negative except during bleeding phases.²⁴² The patients bruise more easily than normal persons and occasionally show large ecchymoses which require a long time to disappear.²⁹¹ Small bruises in hemophiliacs tend to have a hard raised blanched center surrounded by discoloration.²⁹² Such ring shaped suffusions may become concentric rings if the central bleeding recurs. If it stops the periphery may continue to extend into the surrounding tissues. Large hematomas of the scalp are often seen. It has already been mentioned that small skin wounds do not bleed excessively. Even minor operations like lancing

²⁹²Birch C. L. Hemophilia. Illinois Medical and Dental Monographs No. 4. University of Illinois 1937.

²⁹¹Émile-Well F. Hémophilie. Nouveau traité de médecine. Publié par M. H. Roger. Fernand Widal and P. J. Trésier vol. IX 1931. Masson & Co.

²⁹³Butloch and Fildes. Hemophilia. Transactions of the Royal Society of Medicine. Galton Laboratory University of London Part V and VI 1936. 1938. London 1911. Cambridge University Press.

of an abscess have been done without excessive bleeding. However, circumcision, tooth extractions, small furuncles, vaccination, pustules, blows on the nose and biting of the tongue have often caused serious or fatal bleeding. Small injuries in the mouth may develop constantly growing clots which fill the whole mouth and protrude like a huge tongue. Similar growing clots can be seen on the skin. A rare incident is dry gangrene of a foot with spontaneous amputation without bleeding as seen in the case of a boy.³³²



Fig. 3 — Hemophilia. A small furuncle was followed by a deepening hemorrhage which lasted for five weeks. The picture shows the crust eight weeks later. (Courtesy Dr. O. L. Birch and University of Illinois Press. Monograph on Hemophilia.)

According to some older authors the hemorrhagic tendency decreases in the adult age but the majority of the hemophiliacs bleed to death in childhood, sometimes at birth from the umbilical cord. More recently the decrease of the hemophilic tendency in advanced age has been denied.³³³ Periods of in-

creased hemorrhagic tendency sometimes alternate with almost normal periods. Spontaneous hemorrhages frequently recur in cycles of three to six weeks. Spontaneous hemorrhages have occurred in the early spring, less severe ones in the



Fig. 35.—Hemophilia. The patient suffered a small cut in the mucous membrane of the lip. A day later he began to bleed and continued for eight days. The swelling of the lip and the large clot made it impossible for the patient to eat so that he had to be fed liquid through a syringe inserted into his mouth and directed toward the hard palate. The passage of a nasal tube and rigorous proclivity in a hemophilic (Courtesy Dr. G. L. Birch and University of Illinois Library Monograph on Hemophilia).

fall. Hemorrhages may continue for days and weeks with tremendous loss of blood. The immunity of women is probably not an absolute one since a hemorrhagic tendency, especially from the uterus, has been claimed in some females.³³⁴

Émile Weil, Opitz and Zweig after Gottron¹³¹ see review of older evidence in Bulloch and Fildes)²⁵³⁵ Birch²⁵³² gives a long list of bleeding females of hemophilic families but she considers none of them as a true case of hemophilia.

No effective treatment of hemophilia is known but injections of blood plasma, human and animal serum and human placental extract may tide the patient over a critical period. Several substances have been prepared from blood

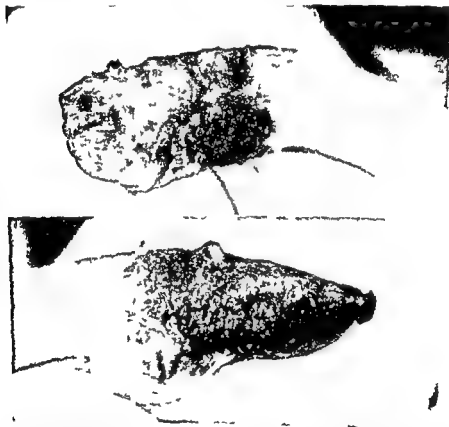


Fig. 39 - Hemophilia. Gargling of the foot which followed an external wound on the right lower abdominal wall and the entire right leg. The foot was later almost entirely without the loss of a single drop of blood. (Courtesy Dr. C. L. Birch and University of Chicago Monograph on Hemophilia.)

and plasma which are able to decrease the clotting time of blood. Nadeau, Lopis, a vegetable vitamin and calcium phosphate preparation, has been little heard of during the last fifteen years. Many preparations have had the same fate. Pressure applied to a wound tends to stop or diminish rounding subcutaneous hemorrhage.²²² Several hereditary conditions resembling true hemophilia but differing either in hereditary transmission or in findings have been described. They are all of little dermatological importance.

Pseudohemophilia is a rare hereditary disease which unlike true hemophilia occurs in and is transmitted by both sexes. The disease may be carried without manifestation.

The symptoms are like those of hemophilia but mostly milder especially later in life. The condition may disappear as the patient grows older. Epistaxis, easy bruising and ecchymoses are common but purpura and petechiae have not been seen.^{2,24} Macfarlane²⁵ has shown in capillaroscopic photography that



Fig. 230.—Hemophilia. Extensive hemorrhage after a tiny furuncle of the right cheek. (Courtesy Dr. G. L. Birch and University of Illinois Press. Monograph on Hemophilia.)

the capillary loops are partly distorted and do not retract after puncture so that bleeding continues in spite of normal blood platelets, coagulation time, clot retraction and tourniquet test. The bleeding time is prolonged.

Hereditary (familial) purpura simplex is much more common than hemophilia. It is more often found in women than in men. The platelet counts, the bleeding, coagulation and clot retraction times are mostly normal but the

²²Minot, C. R. A Familial Hemorrhagic Condition Associated With Prolongation of the Bleeding Time. *Am. J. Med. Sc.* 175: 301, 1918.

tourniquet tests are often positive ^{327 2541} The skin manifestations are mainly spontaneous ecchymoses

In *afibrinogenemia* (pseudohemophilia of the German literature) ^{54 2541} an extremely rare anomaly characterized by lack of fibrinogen in the blood all hemorrhagic symptoms of hemophilia including fatal hemorrhage may occur Coinsized ecchymoses around the big joints have been noticed and the patients bruise easily The blood does not coagulate except on addition of fibrinogen ⁴⁴⁴

Osler's Disease

Rendu Osler Weber's disease is a well defined syndrome which is also known as *angiomatosis hereditaria hemorrhagica*

H I Goldstein ⁵⁴⁸ showed in a series of analyses of the accumulated material that up to 1931 about 110 families had become known in which more than 650 cases of the syndrome occurred Since then the number of published cases has become larger There is much discussion about the priority since many cases belonging to the condition had been published before Osler who recognized the triad of telangiectasis hemorrhage and heredity ²⁵⁴⁴

The first visible telangiectases hardly appear before the age of twenty They appear in crops with a certain predilection to the cheeks and lips Since the individual lesions rarely disappear spontaneously their number grows with the age of the patient and may reach several hundred

There are several types of telangiectases Some of the smaller ones show pulsation under weak glass pressure but most of them are venous ^{547 2541} There are also small red hemangioma like papules with or without surrounding dendritic vessels These lesions cannot be blanched by pressure

The telangiectases develop on the mucous membranes too The nasal cavity the tongue and the gums are almost always involved Hemorrhages have been observed from almost all mucosae from the vagina the uterus the bladder the rectum and other parts of the colon from the stomach the bronchi and the larynx but the nasal septum is by far the commonest source of dangerous

³²⁷Witts L J Th Hereditary Haemorrhagic Diathesis *Quart Hosp Rep* III 465-474 1932

³²⁸Davis H H Hereditary Familial Purpura *Simpl & Lancet* 1939 2 1110-1114

³²⁹Davis E H Hereditary Familial Purpura *Simpl & Lancet* 1941 1 145-146

³³⁰Patley P H and M Alpi K H Familial Purpura Report of Two Cases *Am J Med Sc* 190 263 69 1935

³³¹Roosling E Leberfunktionsstörungen bei hereditärer hämorrhagischer Diathese *Acta med Scandinav* III 104 11 1929 *Zbl* III 351

³³²Rabe H and Salomon E Leberfunktionsstörungen im Blute bei einem Fall von Hämophilie *Deutsches Arch f klin Med* 132 240 19 0

³³³Opit H and F i M Leber eine neue Form der Pseudohämophilie *Jahrb f Kinderh* III 374 1921

³³⁴Macfarlane R G A Boy With No Fibrinogen *Lancet* 1935 1 309

³³⁵Goldstein H I Hereditary Multiple Telangiectasia Goldstein's Hereditary Familial Angiomatosis With Familial Hemorrhages (Rendu Osler Weber's Disease) *Arch Dermat & Syph* 26 25 309 1932

³³⁶Barrook J J Hereditary Hemorrhagic Telangiectasia *Wisconsin M J* 42 805 899 1944

³³⁷Weber F H Haemorrhagic Telangiectasia of the Osler Type *Cas Brit J Dermat* 45 187 193 1936

³³⁸Pardo-Castillo A and Farfán E H Hereditary Multiple Telangiectasia *Arch Dermat & Syph* III 1075-1034 1939

hemorrhages. Death either during the attack of untractable epistaxis or by severe secondary anemia caused by the repeated attacks has often been reported but cases without the dangerous hemorrhagic tendency are known²⁴⁹. Heredity is the third characteristic of the syndrome. Unlike hemophilia the condition is not sexbound and it is transmitted by both sexes following a dominant pattern of heredity.

Besides changes caused by secondary anemia the blood findings are normal especially with regard to bleeding and coagulation time. The affected capillaries have lost their contractility on injury.²⁴¹ Splenomegaly and swelling of the liver occur frequently.²⁴⁹⁻²⁵² Scherer²⁵³ observed cirrhosis of the liver in both mother and daughter with Osler's disease. This is interesting in view of the vascular spiders which are common in hepatic cirrhosis.

Capillaroscopy reveals excessive richness of surface capillaries and lengthening or tortuosity of the loops.²⁴¹ Bommer²⁵⁴ saw aneurysms in great number but never in the retina.

The histology shows the weakness or hypoplasia of the connective and elastic tissue explaining the bulging and vulnerability of the small vessels. The condition must be considered as a systemic hereditary disorder of the entire connective tissue system.²⁻⁴

The therapy is mainly limited to the destruction of the individual lesion by cautery. This operation reportedly often fails to stop the bleeding. Houser²⁵⁵ and Fitz Hugh⁵ advise against blood transfusion if spleen and liver are enlarged.

In several patients with Osler's disease some of the telangiectases of the mucous membranes were seen to diminish or disappear entirely on treatment with moccasin venom.²⁵⁻³

Thrombocytopenic Purpura

Thrombocytopenic purpura is also known as morbus maculosus haemorrhagicus or Werlhof's purpura. Its main feature is abnormal bleeding which may occur in any organ the skin almost never being spared. All mucous membranes especially those of the nose the mouth the lungs the genitourinary and the digestive tracts may ooze blood in varying degrees of severity. Cerebral and adrenal hemorrhages occur. The onset is often sudden without any premonitory symptoms. The course may be hyperacute acute chronic or intermittent. The disease may terminate in complete restitution or in death from hemorrhage or from aplastic anemia caused by the repeated attacks. No

²⁴⁹ Milbradt W. Erfolgreiche Lebertrepanation bei einem Fall von Teleangiectasia haemorrhagica Hereditaria (Osler's Disease) mit Leberstörung. Arch f Dermat u Syph 166 34-40 1933

²⁵⁰ Milbradt W. Atypisch diffuse Sklerodermie mit Oslerischem Syndrom und Leberstörung. Dermat. Wochenschr 99 973-979 1934

²⁵¹ Roenthal. Oslerische Krankheit. Zbl 40 720 193

²⁵² Fitz Hugh T. Jr. Splenomegaly and Hepatic Enlargement in Hereditary Hemorrhagic Telangiectasia. Am J M Sc 181 61-69 1931

²⁵³ van Bogaert L. and Scherer H. J. Hémangiomatose familiale de Rendu Osler et cirrhose hépatique. Ann de méd 111 290-300 1935

²⁵⁴ Roethel P. and Unna P. Über das Wesen der Oslerischen Krankheit. Klin. Wochenschr 12 865-868 1933

²⁵⁵ Houser H. M. Hereditary Hemorrhagic Telangiectasia. Ann. Otol. Rhin. & Laryng 42 731-738 1934

age is immune but children and adolescents especially girls in puberty are more likely to become afflicted and their cases are more often acute. The typical blood findings are low platelet count and increased bleeding time up to ninety minutes. The coagulation time is normal or only moderately increased but the clot does not retract. The coagulated blood remains in a jelly like condition. The tourniquet test is positive. Anemia and abnormalities of the leukocytic picture are absent.⁶ The spleen is often enlarged and tender.

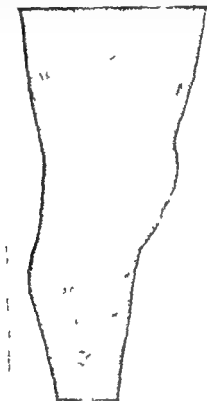


Fig. 331 — Thrombocytopenic purpura. Allergic to streptolysin. (Courtesy of E. H. Urbach.)

Thrombocytopenic purpura is either an entity of its own, the cause of which is unknown, or it is caused by a known factor such as infection, blood dyscrasia, poisoning or liver disease. E. Frank called the idiopathic type essential thrombopenia (thrombocytopenia) to separate it from similar hemorrhagic diseases secondary to other conditions. There is no dermatological difference between these two groups. Essential thrombocytopenia is a rare disease. Only about 149 cases were counted in 275,000 admissions in two American and one European hospitals. These figures probably include some secondary cases. The belief is gaining ground that only the shortcomings of the present diagnostic means create what is known as essential thrombopenic purpura.

⁶⁶Rosenthal, N. (1930). Treatment of Thrombopenic Purpura. J. A. M. A. 112: 101-106.

Dermadromes—The cutaneous purpura appears in crops of varying abundance and on slight local trauma. A ready tendency to bruise particularly over the shins and knees is often the first intimation of the disease¹⁹⁰. The purpuric spots frequently appear first on the legs and they may be restricted to the legs in less severe cases. More often the crops gradually cover the whole body. Petechiae and suffusions are usually seen simultaneously. The mixture of both types of hemorrhagic lesions in the same patient is considered a characteristic feature of the morbus Werlhof¹⁹¹ but this should not be taken too literally. Some cases at least at certain times show only mucosal lesions. The fresh suffusions are not always purely hemorrhagic. When they appear they some



Fig. 332—Acute purpura with thrombocytopenia

times have an *urticarial* character being pink and elevated and show their hemorrhagic nature more clearly only later. Such cases which are on the border line of the anaphylactoid form of purpura are rare. They may be associated with edema of the ankles. Suffusions can easily be produced by gentle flicking bumping or pinching. They sometimes appear on areas which are exposed to pressure e.g. the buttocks or the shoulders. The petechiae can be provoked by increased venous pressure by coughing pressing during a bowel movement etc. They appear as deep purple sharply outlined pin point or lentil sized spots sometimes lined up in streaks from scratches.

Change from the horizontal to the upright position may produce purpuric lesions. This phenomenon known as orthostatic purpura is often marked in patients who are just recovering from an attack of thrombopenic purpura. It can be observed in other types of purpura too.

Purple or black spots or suffusions especially of the gums and of the oral or pharyngeal mucosa are quite common.³²⁷ This diapedetic bleeding from the mucous membranes may create a very serious condition.

Pathogenesis—Thrombopenia and abnormal bleeding are the outstanding signs of Werlhof's disease. Since the blood platelets are born in the bone marrow and die in the reticulo endothelial system especially the spleen their population in the blood can be influenced from both ends. Depression of the bone marrow by bacterial and other poisons by radiant energy carcinomatosis and other local processes may thus result in the same thrombopenic and purpuric effects as hyperactivity of the spleen. The spleen may be thought of as devouring the platelets or as exerting a depressing influence on the megakaryocytes in the bone marrow possibly by means of a hormonal mechanism. (For discussion of the experimental evidence see Quick³³⁰). It has long been observed that however striking the thrombopenia in Werlhof's purpura may be no definite parallel between platelet count and purpura exists. Sometimes bleeding occurred in moderate thrombopenia and in some cases purpura did not appear with very low platelet numbers³³¹ or the platelet count decreased only after the hemorrhage.²⁴⁶ Macfarlane²⁰³ showed in capillaroscopic photographs that the injured capillaries did not retract in thrombopenic purpura. These and many other observations show that the vascular reaction more precisely the lack of vasoconstriction after injury is an important factor. Quick³³⁰ tried to connect the platelet and the vascular theories. The capillary dilation is caused by histamine and one of the functions of the platelets is to remove this agent which is formed in excess. In carrying out this task the platelets are rendered more susceptible to agglutination and lysis. This hypothesis which is based on considerable evidence would explain vasodilation as well as loss of platelets. The spleen or the reticulo endothelial system is possibly a major source of the histamine which kills off the platelets. The opinion that allergy plays a part in thrombopenic purpura is gaining favor and is expressed in the tendency to remove the borderline between thrombopenic and nonthrombopenic purpura. The main reasons for an allergic theory of thrombopenic purpura are based on the great number of cases which have been observed after prolonged and repeated medication with arsphenamine gold³³² edormid²⁴⁰ quinine nirvanol and after ingestion of cow's milk³³³ and other foods. Infections for example pertussis have caused thrombopenic purpura so have blood transfusions.³⁶ ³³⁴

³²⁷Watson Williams E. The Fatal Lesions of Purpura. *J. Laryng. & Otol.* 53: 181-186, 1938.
³²⁸Rokkam J. Purpuras hémorragiques et thrombopénie. (Étude expérimentale). Pathogénie du syndrome hémorragique engendré par l'administration de sérum antiplaquettes. *Sang* 5: 129-169, 1934. *Zbl.* 48: 400.

³²⁹Hulson E. H. Purpura Haemorrhagica Caused by Gold and Arsenic Compound. *Two Cases*. *Lancet* 2: 74-77, 1935.

³³⁰Hol H. H. Purpura From Sedormid. *J. A. M. A.* 113: 674-675, 1939.

³³¹Lauberg R. M. Purpura nach Kubmilch. *Ztschr. f. Kinderh.* 39: 369, 1931.

³³²Brinckler H. N. Möbus Werlhof mit allg. toxisch. Reaktion auf mütterliches Blut der gelben Bl. Gruppe. *Ztschr. f. Kinderh.* 61: 566-578, 1931.

³³³Quill T. D. and Madison F. W. Purpura and Food Allergy. *J. A. M. A.* 106: 402, 1936.

³³⁴Pat E. A. Jr. Thrombopenic Purpura and Other Hemorrhagic Diseases. *Am. J. M. Sc.* 191: 7-13, 1936.

Other reports are inconclusive because of small numbers or not comparable because of great differences in technique.

Rudisill⁷² and also Mettler and Stone⁷³ believe that roentgen-radiation is valuable (8 cases) in thrombopenia. Doses at 200 r per sitting applied to the spleen with low intensity and heavy filtration are recommended. About six treatments may be given with three days interval. The platelet count has been seen to rise after the first treatment. Most of the chronic cases are now operated upon, the cases with poorer prognosis being left to other methods.^{71, 74, 77} X-ray therapy is less reliable than splenectomy, but practically without danger. It may well tide a patient over a critical phase.

Blood transfusions are of great but only palliative value. Rosenthal⁷⁵ sees no value in repeated small transfusions. Vitamins C and B, parathyroid extracts and Stryphnon⁷⁶ have been advocated. Mocassin snake venom⁷⁷ is of some palliative value in chronic cases.⁷⁶

Schonlein-Henoch's Non-thrombocytopenic or Anaphylactoid Purpura

After separating the thrombocytopenic purpura a group of purpuras remain which—though not without exceptions⁴⁶¹ has normal platelet count, normal bleeding and coagulation times and normal clot retraction. Usually the tourniquet test is positive.³⁵⁰ Allergy and infection have been increasingly found to be significant in their pathogenesis. The combination with other symptoms which are well established allergic phenomena like urticaria, angioneurotic edema and swelling of the joints is reflected in the term anaphylactoid.²⁵¹ Today the group would probably be called allergic purpura. However, there are many cases in which no allergic or infectious cause can be detected.

In *Schonlein's purpura* as the anaphylactoid purpura has been and still is called, the urticarial component is a characteristic feature. Glanzmann²⁵¹ used the term *purpura urticaria* for raised white or pink small or large wheals. The petechiae often develop within the urticarial and slightly inflammatory lesions. While the urticarial element quickly disappears the hemorrhagic part stays and undergoes the well known changes.

⁷²Rudisill H Jr. Successful treatment of Essential Thrombopenia With Hemorrhage by Roentgen Ray. *JAMA* 107 119 120 1936

⁷³Mettler S R and Stone R G. Effect of Roentgen Ray Irradiation on Platelet Production in Experimental Thrombocytopenia. *Am J Med Sci* 191 94 107 1936

⁷⁴Hippe H and Lechmann R. Die Behandlung der thrombopenischen Purpura im Kindesalter mit Röntgenbestrahlung. *deutsche Wochenschrift für Kinderheilkunde* 126 307 309 1937

⁷⁵Wittob M M Haffaha M J and Thomas C M. Purpura Haemorrhagica With Special Reference to Course and Treatment. *JAMA* 109 11 10-1176 1937

⁷⁶Histolf G. La roentgenotherapie des malades à syndrome hémorragique. *Radiol med* 19 773 80 809-833 1937

⁷⁷Hirk W. Ichweidelexigeneur Röntgenbehandlung der kinderskrankheiten und über die Frage der Röntgenstrahlung bei med. Wochenschr 1931 II 1719 1720

⁷⁸Hirsh R. Die Behandlung der thrombopenischen Purpura im Kindesalter. *Wochenschr* 1936 I 935-937

⁷⁹Peck G M and Rosenthal W. Effect of Mocassin Snake Venom (Anelastrodo placivorus) in Hemorrhagic Condition. *JAMA* 104 1066 1931

⁸⁰Golst F. Schönlein-Henoch's Purpura. Report of a Case With Review of the Literature. *Clin North America* 12 869-881 1937

⁸¹Glanzmann H. Purpura Fulminans. *Schw. med. Wochenschr* 67 829 830 1937

Erythema nodosum and erythema multiforme like eruptions have been observed. The pleomorphic character of the lesions is supposed to be an outstanding feature.²³⁸⁰ The lesions appear in crops predominantly over the lower legs. Less frequently the other parts of the body are involved. The face, the bends of the large joints and the palms and soles usually remain free.²³⁸¹ The crops follow each other in intervals of days or weeks. Recurrences have been observed years after apparent healing.

The spring of the year seems to favor the first outbreak as well as recurrences. The term purpura (peliosis) rheumatica refers to the combination of purpura with painful mostly serous exudations into the joints. They have nothing to do with rheumatic fever.

Henoch's purpura is an anaphylactoid purpura with acute hemorrhagic intestinal symptoms. Heartburn, epigastric discomfort, abdominal colic, nausea and vomiting, melenic constipation or more often diarrhea with bloody stools and other symptoms of acute abdominal disease are usually present and have not infrequently led to a diagnosis of appendicitis or intussusception with subsequent laparotomy.²³⁸² Purpuric skin lesions in acute abdominal conditions, especially in children, should make the possibility of Henoch's purpura enter the physician's mind. There are showers of petechiae on the skin²³⁸³ and polymorphous skin lesions similar to those in Schönlein's purpura to which Henoch's purpura is related. Unfortunately the purpura often follows the abdominal symptoms by several days which complicates the matter and explains the diagnostic errors.

The allergic character of many cases of Schönlein's and Henoch's purpura has been demonstrated.²³⁸⁴ Improvement after elimination of wheat²³⁸⁵ eggs and wheat²³⁸⁶ and a number of other items like pork, milk, potatoes, chicken, etc.²³⁸⁷ has been observed. Allergic diseases in the family, hay fever, infantile eczema and preceding allergic diseases are more common than one would expect.²³⁸⁸ The relationship to urticaria, angioneurotic edema, joint swellings and the resemblance to serum sickness has often been emphasized. Accompanying infection is just as common. Tuberculosis, tonsillitis,²³⁸⁷ scarlet fever,²³⁸⁹ prostatitis (O'Leary in discussion of Caro and Zeisler²³⁸⁹), malaria tropica²³⁹⁰ may be mentioned as a few examples.

Purpura fulminans is a rare fatal hemorrhagic disease which occurs in severe, mostly septic infections. The patients are almost always children. While infections with pneumococci as well as scarlet fever and measles have occa-

²³⁸²Alpert, H. B. Allergic Purpura and Acute Abdominal Symptoms. *Med. Rec.* **154**, 1822, 1941.

²³⁸³Kahn, I. M. Henoch's Purpura Due to Food Allergy. *J. Lab. & Clin. Med.* **11**, 835-836, 1919.

²³⁸⁴Baethlein, F. L. Allergic Purpura. *J. Allergy* **1**, 170-171, 1930.

²³⁸⁵Alexander, H. L. and Eymann, C. H. Allergic Purpura. *J. A. M. A.* **111**, 209, 2094, 1919.

²³⁸⁶Eymann, C. H. Henoch's Purpura. *South. M. J.* **28**, 341, 1935.

²³⁸⁷Coke, H. Two Interesting Cases of Purpura. *B. M. J.* **3**, 3664, 535-537, 1931.

²³⁸⁸Iratt, T. A. and F. W. H. W. O. Purpura Fulminans Following a Mild Case of Scarlet Fever. *Brit. M. J.* **3**, 560, 595-596, 1929.

²³⁸⁹Caro, M. R. and Zeisler, E. P. Recurrent Chronic Purpura. *Arch. Dermat. & Syph.* **24**, 70, 703, 1931.

²³⁹⁰Burhanettin, Z. Ein Fall von Malaria mit Henoch-Schönlein bzw. Wehlofsche Purpura. *Dtsch. B.* **265-267**, 1937. *Zbl.* **57**, 439.

sionally been followed by fulminating purpura the majority of the cases were observed in the course of meningitis

The ecchymoses in purpura fulminans occupy large areas e.g. entire extremities and sometimes almost the whole skin. These giant lesions develop very rapidly often in a few hours. The involved areas are sometimes entirely black. A certain symmetry of the purpuric lesions is striking in some cases. The platelets bleeding time coagulation time clot retraction and fibrinogen were normal in Glanzmann's case. The autopsy findings are mostly negative.²⁵¹ This is not the case in a group of fulminating purpuras which now can well be separated and which is known as the *Waterhouse-Friderichsen syndrome*.^{251, 252} Only about sixty cases have become known since Marchand (according to Glanzmann²⁵³) in 1880 first observed a case of this kind. The terminology should give credit to Little²⁵⁴ who in 1901 ten years before Waterhouse and seventeen years before Friderichsen published twelve cases the greatest contribution of a single author.

The syndrome occurs mostly in children younger than one year but it has been seen in adults.²⁵⁵ The onset is very sudden often with abdominal pain and vomiting moderate fever and flushed face. The patient soon becomes stuporous this may be mistaken as healthy slumber.²⁵⁶ After ten to twelve hours cyanosis which may alternate with ashen gray pallor is striking. In this stage showers of petechiae may appear over the whole body. The purpuric spots increase rapidly sometimes under the very eyes of the observer. They may coalesce and produce a blotchy appearance. On the buttocks back and extensor surfaces of the arms they may look like postmortem lividity. The rash remains until death. Rarely the petechiae stay small. According to Aegerter²⁵⁶ no skin lesions showed in thirteen out of fifty seven cases.

Headache and other symptoms of the nervous system profound weakness spiking temperatures from subnormal to 108°F low blood pressure and circulatory disturbances are often mentioned. Cervical rigidity is usually absent. Almost all patients died within a day or two. The diagnosis is rarely made ante mortem. Leukocytosis is mentioned in seven cases.²⁵⁶ In two cases^{251, 257} the platelet counts were extremely low in two others normal. Most of the other cases do not mention hematological findings.²⁵⁶ Coagulation and bleeding time have been found normal several times. Hypoglycemia and elevation of nonprotein nitrogen of the blood has been described.²⁵⁶ At autopsy the out-

²⁵¹ Waterhouse W A Case of Adrenal Apoplexy Lancet 1911 4 577-578

²⁵² Friderichsen C Neb nierenapoplexie bei kleinen Kindern Jahrb f Kinderh 87 109 1 5 1918

²⁵³ Glanzmann E Beitrag zur Klinik Hämatologie und Pathologie des Syndroms von Waterhouse-Friderichsen (Neb nierenapoplexie bei kleinen Kindern) Jahrb f Kinderh 129 49-63 1933

²⁵⁴ Little H G Case of Purpura Fulminans Fatally Associated With Hemorrhage Into Suprarenal Capsules Brit J Dermat 11 445-467 1901

²⁵⁵ Thomas H B & Lelphart C H Hemiplegia and Purpura With Adrenal Hemorrhage in the Adult JAMA 123 941-950 1934

²⁵⁶ Aegerter E F The Waterhouse-Friderichsen Syndrome A Review of the Literature and a Report of Two Cases JAMA 106 1715 1 19 1936

²⁵⁷ Leinonen A A Waterhouse-Friderichsen Syndrome Case With Autopsy Findings J Pediatr 18 500-516 1939

²⁵⁸ Leber G J Waterhouse-Friderichsen Syndrome Canad M A J 38 232 1939

standing finding in 95 per cent of the cases was destructive bilateral adrenal hemorrhage. Often no adrenal tissue could be made out.

It is now certain that most of these cases are caused by meningococcic infection probably with a massive invasion of meningococci into the blood stream. Just as in other rashes of meningococcic disease meningococci have been found in the purpuric lesions.^{399 400}

Purpura annularis telangiectodes Majocchi and Schramberg's disease, two related purpuric skin diseases, have some internal relationship. (See Polycythemia.)

Recently E. Davis⁴⁰¹ has given a statistical analysis of 500 consecutive cases of purpura. This large series provides an index of the frequency of the various types of purpura. The diagnosis of purpura simplex was made in 15 per cent, Schönlein's purpura in 2 per cent, Henoch's in 0.4 per cent, hereditary familial purpura simplex 15 per cent, primary thrombocytopoenia 0.8 per cent, hemophilia 0.2 per cent and pseudohemophilia familial or nonfamilial in 1 per cent. The rest (63 per cent) was grouped under the many types of symptomatic purpuras in infections, poisonings, etc.

³⁹⁹McLean, Wt. and Caffey, J. Definite Purpuric Meningococcic Hemorrhagia. Early Life Diagnostic Value of Smears from Purpuric Lesions. *Am J Dis Child* 42: 103, 1931.

⁴⁰⁰Latta, G. Quale di un caso di porpora fulminante. *Pediatria (It)* 39: 333-341, 1931.

⁴⁰¹Davis, F. Purpura of Skin. *Quart J Med* 1933, 2: 160-161.

CHAPTER XXXV

DERMADROMES OF INTERNAL CANCER

Internal cancer may manifest itself on the skin by *metastases* by *nonspecific dermadromes* and by *acanthosis nigricans* ⁶⁰

Cutaneous Metastases — It can generally be said that only mammary cancer in advanced stages as well as occasionally after the operation of cases on the borderline of operability, reach the skin frequently by direct extension by operative implantation or by lymphatic metastases

The contiguous metastases appear as painless nodules which grow rapidly and if dense enough coalesce into large hard masses which may surround the chest wall like armor (Cancer en cuirasse). Sometimes the diffuse invasion of the skin forms an evenly red sharply and jaggedly outlined area of inflammatory cancer which is known as *erysipelas carcinomatosum*

Skin metastases from visceral cancers are rare probably occurring not more often than in 1 ⁶⁰¹ to 3 per cent ²⁸⁰⁴

Since there is no flow of lymph directed from the viscera toward the skin the metastases are likely to originate from a primary lesion or still more often from secondary cancers in the lungs ⁶⁰² or in the liver. This fact accentuates the *ominous significance* of all skin metastases of visceral cancer

Adenocarcinoma of the stomach occasionally produces an outcropping of hard mostly red nodes scattered in moderate numbers over the skin. Firm scleroderma like plaques in the skin have also been seen ^{260 2606}. Dermal secondaries of hypernephromas prostatic or breast ⁶⁰⁶ cancers have been found in the scalp suggesting sebaceous cysts ⁶⁰⁷ or turban tumors ⁶⁰⁷. The upper abdomen and the umbilicus have relatively often been seen to develop metastatic growths originating from the stomach ovary or uterus. They are direct subsidiaries of metastatic nodules in the liver from which they travel through the ligamentum teres ⁶⁰⁴⁻⁶⁰⁶

Rectal carcinomas may develop sessile or pedunculated metastases about the buttocks ⁶⁰⁷. Only a few cases of cutaneous lesions from ovarian carcinoma have been reported ¹⁴⁴⁸. Several of the cases showed firm plaques or confluent nodules in an edematous purplish brown skin which were not very suggestive of metastatic cancer. The lesions resembled erysipelas or more correctly the

⁶⁰¹Rothman H. L. f. Hauterscheinungen bei bösartigen Geschwülsten in inneren Organen Arch f. Dermat u. Syph 149 99 1 3 1927

⁶⁰²Walthers H. E. Metastases of Cutaneous Carcinoma and Secondary Skin Tumors Schweiz med. Wchnschr 71 99 100 1941

⁶⁰³Gates O. Cutaneous Metastases of Malignant Disease. Am J Cancer 20 718 729 1937

⁶⁰⁴Bade W. Das metastatische Carcinom der Haut im Anschluss an Carcinom innerer Organe Arch. f. Dermat u. Syph 179 7 4 1939

⁶⁰⁵Ronchese M. Metastases of the Scalp Stimulated by Turban Tumors Arch. Dermat. & Syph 41 639-645 1940



Fig. 333 — Ulcer in metastases from cancer of the stomach



Fig. 334 — Skin metastases from cancer of the stomach

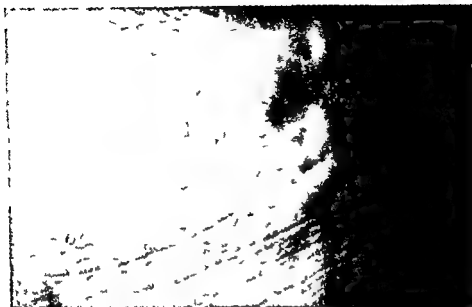


Fig 33 --Lymphosarcoma cutaneous metastases, forehead



Fig 33b --Skin metastases from lymphosarcoma

erysipelas carcinomatosum of the breast. The biopsy, however, revealed metastatic ovarian carcinoma. Bronchial carcinomas metastasize to the skin relatively often.⁶⁰³

A rare event is the hematogenous spread of a cancer developing from the epithelial lining of an *osteomyelitic sinus*. Crops of metastatic nodules have appeared in the skin of the upper arm after the amputation of an osteomyelitic finger.⁶⁰⁴



Fig. 337.—Crops of metastatic nodules of the lymph

Lymphosarcoma and melanosarcoma are probably more apt to metastasize to the skin than the other more common cancers. They both form cutaneous and subcutaneous nodules or plaques which in some cases appear on the surface in enormous numbers. The metastases of melanoma are in one out of three cases entirely or partially pigment free (amelanotic); the melanotic character of the cells being demonstrable only by the positive dopa reaction.⁶⁰⁵

⁶⁰³Stewart C. D., Obermayer M. E. and Woolhandler H.: Cutaneous Metastatic Carcinoma Originating From Osteomyelitic Cavities. *Arch. Dermat. & Syph.* 41: 545-50, 1910.

Conclusions with regard to the *site of a primary tumor* from the distribution or clinical appearance of skin metastases are less reliable than the pathologic picture

The skin does not seem to offer a good soil for the cancerous seeds. Skin nodules have been seen to disappear *spontaneously*^{609 610} and they usually appear quite *radiosensitive*; this can be interpreted as a lack of vitality. A few hundred roentgen units may make them disappear but of course there is no more than palliative benefit for the patient from treating metastases. However it is not true that cutaneous metastases indicate a particularly fast rate of growth of the primary tumor or that they herald approaching death. The patients may still live many months or even years.^{604 611} Three years of life have been recorded in a case of adamantinoma of the mandible after distant metastases had appeared on the temple.⁶⁰⁴ Three to six months is the average time a patient will live after the appearance of skin metastases.

Nonspecific Exanthem—A still rarer dermatome of internal cancer is the *nonspecific exanthem*. These eruptions range from simple pruritus and prurigo like eruptions with hyperpigmentation to bullous, multiform and eczematoid rashes. Typical dermatitis herpetiformis,⁶⁰ lupus erythematosus acutus, pellagroid and exfoliative dermatitis,⁶¹ generalized urticaria,⁶¹² purpura,⁶¹⁴ and purpuric dermatitis with widespread superficial necrosis are on record.^{610 61} Thrombocytopenic purpura⁶¹⁶ may be caused by massive invasion of the bone marrow by metastases. In some cases,⁶¹⁷ a generalized polymorphous exanthem was seen in x-ray treated malignancies of the mouth and neck. Drug eruptions from barbiturates are difficult to rule out in some of these instances.

The rashes especially pruritus may precede subjective or objective signs of cancer and they may disappear after successful removal of the neoplasms.⁶¹¹ The peculiar tendency to multiple peripheral thromboses and short clotting time in pancreatic cancer have been mentioned (see pancreas). The exanthems in internal cancers are interpreted as reactions to metastasized tumor cells which have been destroyed by cutaneous defense mechanisms.⁶¹³

Diffuse deep *bluish black discoloration* of the face, neck and hands together with melanuria in a case of widespread metastases of a malignant melanoma was

⁶⁰⁹ Szary A, Horowitz A and Milet A. Epithéliomas en metastases de la peau. Bull. Soc. f. a. c. d. dermat. et. syph. 40: 191-193, 1933.

⁶¹⁰ Du Roi. Ca. c. r. d. la. la. gu. t. m. t. las. a. cutane. Schweiz. med. Wchnschr. 1928 II: 1051-1059.

⁶¹¹ Kaufman Wolf M. Histopathologie des A. h. l. s. s. Carcinom. In: e. e. O. Kane. Arch. f. Dermat. u. Syph. 114: 707-744, 1913.

⁶¹² Schw. gl. R. Frythrode m. l. u. l. l. t. ru. Carcinom. Zbl. f. Gynäk. 57: 94-99, 1913.

⁶¹³ L. rhach F. Enloxe ou All. rgy. Arch. Dermat. & Syph. 45: 637-722, 1942.

⁶¹⁴ Stillman R. G. Col. liene. of M. ligu. nt. Tumor and Purpura Hemorrhagica. M. Clin. North America 14: 1533-1574, 1931.

⁶¹⁵ Becker A. W. Kahn D. and Rothman G. Cutaneous Manifestations of Internal Malignant Tumors. Arch. Dermat. & Syph. 45: 1062-1069, 1944.

⁶¹⁶ Blum I. L. be. symptomatic Thrombop. i. b. i. Magen. Carcinom. Med. Klin. III: 1200-1204, 1924.

⁶¹⁷ Low L. and Camil I. M. R. F. anth. m. Complicati. g. Neoplastic Disease. 4 Cases. Am. J. Roent. nol. 43: 547-596, 1940.

seen by Odel Montgomery and Horton¹¹⁸ The authors assumed involvement of the adrenal glands and chromaffin tissue

The eruptive appearance of senile *hemangiomas* (ruby points) in relatively young persons has been *disproved* to be suggestive of visceral cancer¹⁵⁹ Schridde¹¹⁹ claimed that the occurrence of dark pigmented coarser hairs of dull surface especially on the temples but also in the eyebrows and beard were indicative of cancer They were even found among blond and gray but not among red hairs This claim still lacks confirmation

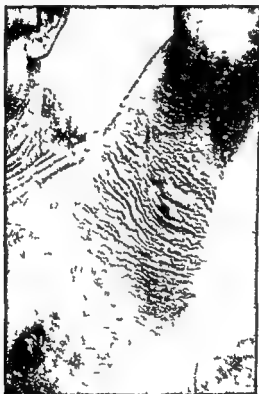


Fig. 334 — Acanthosis nigricans (Courtesy Dr. M. Jessner)

Acanthosis nigricans is a dermatosis of remarkably uniform appearance The disease is rare about 400 cases have been recorded since S. Pollitzer¹²⁰ in collaboration with P. G. Unna published the first case in 1890 (see also Pollitzer¹²¹) The significant elements of the gross skin changes are a characteristic *distribution papillary hypertrophy hyperpigmentation and hyperkeratosis* The sites of predilection are the axillae the nape of the neck the genitals the inner

¹¹⁸Odel H. M. Montgomery H. and Horton H. T. Diffuse Melanosis Secondary to Malignant Melanoma Proc. Staff Meet. Mayo Clin. 12: 742-747, 1937

¹¹⁹Schridde H. Kr. b. Haare. M. d. ch. n. med. Wchn. chr. 69: 1565-1566, 19

¹²⁰Pollitzer S. Internat. Atlas. selt. Hautkr. 10: 1890

¹²¹Pollitzer S. Acanthosis nigricans. J. A. M. A. 53: 1369-1373, 1909

thighs the elbow bends, the umbilicus the perianal region and the dorsa of the hands and feet. In some cases the lips the anterior neck the areolae of the nipples and large areas of the trunk may also be affected. There is almost in all cases marked symmetry provided the picture is fully developed.

The affected skin is densely covered with mostly smaller than pea size sessile nodules with a more or less rounded top. Many of them especially in the axillae and on the nape are crowded into rows or small groups and separated by the natural furrows of the skin. Among the great number of little papules is scattered a much smaller number of larger ones forming a picture comparable to the fungi form papillae among the filiform papillae of the tongue. In the folds cauliflower or cocks comb resembling growths have been observed.

The color of the lesions varies from gray slate or yellow to all shades of brown and black. The melanosis often extends beyond the papillomatous area. Some times gross hyperpigmentation is missing the lesions then having a yellow orange hue. Depigmentations within the darkened areas are due to inflammation. Scattered nevus like hyperpigmented lesions in apparently unaffected skin are frequent concomitant efflorescences which may appear in great numbers.¹² Scaling dryness or palpable roughness as gross expressions of hyperkeratosis are present but are not prominent features. The palms and soles are often hyperkeratotic^{20, 21} but they remain free of hyperpigmentation. Pruritus is sometimes present.

The disease starts gradually most often under the arms and progresses slowly. The pigmentation is increased by exposure to light the papillary hyperplasia by friction and maceration.

The oral mucosa and the transitional skin of the lips and of the vulva participate in the papillary hyperplasia in about one half of the cases. The dorsum of the tongue may take on a furrowed appearance resembling lingua plicata and the papillae may be enlarged and rough like those of a cat's tongue. Even thin spines have been described.⁶ Similar papillary or granulated surfaces may be seen on the palate the line along the bite on the buccal mucosa the epiglottis and even in the larynx. Mucosal pigmentation is rare but it has been observed often enough to discredit its absence as being a distinguishing characteristic against Addison's disease and other melanoses. The esophagus¹⁴ the rectum and the lower part of the vagina often participate in the process.

The hair is usually destroyed in the affected areas.

The nail beds may be pigmented and the nails longitudinally grooved.

The histopathology reveals enlarged and elongated papillae hyperpigmentation in the basal cell layer acanthosis and hyperkeratosis. A small amount of inflammation is present. Hypertrophy of the sebaceous glands has been noted.⁶

It is customary to distinguish between a benign and a malignant type of acanthosis nigricans. There is no difference in the morphology of the two types.

- ¹²² Moncorpe H. Keratosen Acanthosis nigricans in Handb. d. H. u. G. 8 37-40 1931
²⁰ Kuttner H. Die Acanthosis nigricans und ihre Bedeutung für die Diagnose des malignen Tumors Mitt. d. Grenzgeb. d. Med. u. Chir. 29 278-296 19 6
²¹ Tönnemann H. Über Acanthosis nigricans bei über einen Fall mit Beteiligung der Spina rühre Virchows Arch. f. path. Anat. 279 253-261 1931
²² Yamada K. A Case of Acanthosis nigricans Jap. J. Dermat. & Leif. 25 61 19 5 Zbl. 19

The adjective malignant refers to the association with malignancy, not to a malignant course of the dermatosis itself. The benign type is also often called juvenile because many cases start in early childhood and remain stationary throughout later life. Some of these patients died later of cancer. Some of the juvenile cases were malignant and some adult cases at least clinically were not associated with malignancy.²⁴⁶ Thus there is no sharp borderline between the two types. The etiology and pathogenesis of acanthosis nigricans is far from being understood but there are some facts known which eventually may lead not only to the elucidation of the remarkable phenomena of this disease but also of other pigmentary disorders.



Fig. 339.—Acanthosis nigricans. Obesity. Juvenile. No malignancy. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

The most important etiologic fact is that at least 50 per cent of the cases of acanthosis nigricans occur in patients with cancer. Fully 92 per cent of these malignancies were found in the abdominal viscera, mostly in the stomach.²⁴⁷ Almost all of the nonabdominal cancers had abdominal metastases.²⁴⁷ The course of many neoplasms associated with acanthosis nigricans is highly malignant.

²⁴⁶Burgess N. A Case of Acanthosis Nigricans. *Brit J Dermatol* 43: 169-177, 1931.

²⁴⁷Ollendorff Curth H. Cancer Associated With Acanthosis Nigricans. *Cancer Arch Surg* 47: 517-552, 1943.

In trying to explain the peculiar pigmentary skin disease which has some features of Addison's disease the thought of an adrenal etiology has arisen. However at least twelve cases are on record in which autopsy failed to show any adrenal involvement. H. O. Curth^{26, 27} who has recently reviewed the available material with regard to other endocrine glands arrives at the conclusion that theoretic considerations and actual records of cases speak against endocrine

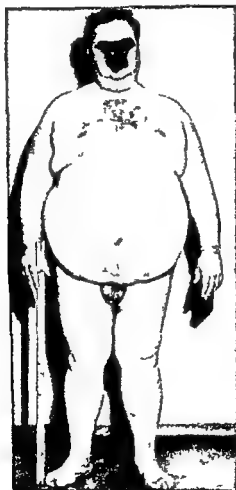


Fig. 340—Obesity of pituitary type in a patient with acanthosis nigricans. (Courtesy Division of Endocrinology, Department of Medicine, University of Chicago.)

disturbances as a causative factor in acanthosis nigricans. Yet a great number and variety of endocrine disorders have been found in association with acanthosis nigricans. It seems that although at the present time no satisfactory endocrinological etiology can be propounded, the described associations with obesity, debility, dwarfism, genital hypoplasia, diabetes, goiter, cryptorchism, achondro-

plasia and acromegaly cannot be slighted. Puberty exerts a provoking influence on the onset or development.²⁶²⁷ Of great interest is the case of Hellerström²⁶²⁸ who observed marked though not complete regression of the diffuse papillomas after castration of a male patient. Ketosteroid determinations do not seem to have been done in acanthosis nigricans. In a few cases the dermatosis subsided after treatment of the cancer and recurred with it (Spieschka after Moncorps²⁶²⁹). Spreading of acanthosis nigricans after stationary periods seems to coincide with the development of cancer.²⁶²⁷ These observations point to the neoplasm itself as a cause. But the great rarity of acanthosis nigricans compared with the frequency of abdominal neoplasms compels one to believe that a rare combination of factors must be required. The same conclusion must be applied to the association with other diseases. The dermatosis usually preceded in some cases for many years the development or at least the discovery of cancer. The etiologic role of the abdominal sympathetic system is not yet clear. Stimulation of the chromaffin system could explain the hyperpigmentation but not the other aspects of the syndrome. Most cases have not been investigated thoroughly from this view point. In one case the resection of a cervical ganglion resulted in rapid regression of acanthosis nigricans in the axillary areas.²⁶³⁰ Ten instances of familial occurrence all of the benign type have been observed.²⁶³¹

The treatment of acanthosis nigricans is at best symptomatic unless regression occurs after extirpation of the malignancy. The prognosis of juvenile acanthosis nigricans as a dermatosis is that of an incurable though in itself not dangerous anomaly comparable to a widespread nevus. However the prognosis of the juvenile benign variety is darkened by the frequent association with systemic disease. The prognosis of the cases starting in the age group from 20 to 40 years is doubtful. Acanthosis nigricans which develops after the age of 40 is almost certain to be indicative of cancer usually visceral²⁶³² which when the dermadrome appears already has metastasized. Exploratory laprotomy is inadvisable (O'Leary in discussion to Michelson²⁶³³).

²⁶²⁷Hellerström G. Zur Kenntnis der Acanthosis nigricans. A. ta dermat. —ve ercol. 11: 86-94, 1933. Zbl. 46: 180, 1934.

²⁶²⁸Moncorps J. C. and Montgomery H. Acanthosis Nigricans a Clinical Malignancy Precursor. Meet. Mayo Clin. 11: 113-117, 1930.

CHAPTER XXXVI

DISORDERS OF THE NERVOUS SYSTEM

The function of the skin as an organ of sense may become affected by disturbances of the peripheral sensory nerves as well as of the central nervous system. Cutaneous secretion, pilomotion, vascular tonus and trophic balance depend on the autonomic nervous system, the functioning of which may be disturbed by local organic lesions as well as by reflexes and hormonal activations originating somewhere else. These considerations give us an idea of the complex mechanisms by which a great variety of noxae including malformations, injuries, infections, poisonings and endocrine disorders may produce dermatomes of neurogenic character.

Cutaneous Senses ^{1325 1326 1331}

A variety of specialized nerve endings gives the skin the character of a sense organ. The perception of all cutaneous stimuli is not diffuse as it seems to be but localized in points which are distributed over the skin in varying density. The end organs related to the sensitive spots are highly specialized in their functions. Thus forcing of a needle into a Meissnerian body does not cause pain but only the sensation of touch. The *warmth* spots are most dense on the face and on the lateral aspects of the fingers (2 per square centimeter). The *cold* spots are much more numerous with the greatest density on the face and on the trunk. About 11 cold spots can be mapped out on one square centimeter of facial skin ¹³³¹. About one third of the body surface is unable to perceive warmth.

Free nerve endings in the epithelium radiating from subepithelial plexuses receive the stimuli causing the sensation of *pain*. The skin has only one quality of pain but differences in intensity and duration may cause such varieties as burning, pricking and soreness. Lewis and Hess ¹³² believe that pain is caused by a substance produced in the tissue and acting on the endings of the pain nerves. This hypothetical substance does not seem to be histamine.

The pain spots are most dense in the popliteal fossa with 232 per square centimeter and least dense on the tip of the nose with only 44 per square cm ¹³³¹. The sense of *touch* is also localized in points which are mostly situated at the hair follicles. The nerve endings surround the follicles like a basket. The bent hair acts as a lever and intensifies the pressure on the end-organs. The hairs widen the perceptive area of the follicle and make the point system appear diffuse. A shaved area is considerably less sensitive to touch than a hairy one ¹³²⁹. The

¹³²⁵Guttmann E. Haut u. d. Nerven-System. Handb. d. H. u. Gk. 4 2 1. 1301. 1933.

¹³²⁶Von Frey M. and R. in H. Physiologie d. r. Haut. Handb. d. H. u. Gk. 2 2. 19 9.

¹³³¹Lewis T. and Hess B. Pain Derived from the skin. Mechanism of Production. J. Neurophysiol. 1933.

sensation caused by a constant stimulus for example the bending of a hair soon fades and is no longer perceived. This phenomenon is called adaptation. Because of adaptation we do not feel the weight of our clothes and a needle prick is painful only for a moment. The pain will stop in spite of the fact that the needle is still sticking in the skin. We do not feel a temperature which does not change.

Nerve Section—The effect of cutaneous nerve section was studied in famous self experiments by Head. Foerster⁴²² in evaluating nerve injuries caused by gun shots during and after the first World War and other authors⁴²³ modified Head's observations to some extent.⁴²⁴ The section of a sensory nerve immediately abolishes all forms of skin sensibility. The areas of thermal tactile and analgetic anesthesia after section of the nerve are not entirely congruous. Section of the ulnar nerve for instance leaves a zone in part two inches in width in which only pain but not touch or temperature can be felt. The disturbance of the perception of temperature is more extensive than that of touch and pain and the loss of the perception of warmth is more extensive than that of cold.⁴²⁵ With the regeneration of the nerve the sensibility returns in two stages. The two stages are explained by some authors by the existence and the difference in the regeneration of two kinds of fibers.⁴²⁶ After seven to thirty weeks a markedly punctate sensibility appears with relatively wide anesthetic areas in between. However the perception of intensities and the localization of a punctate stimulus is inaccurate and radiating widely from the point of stimulation. The threshold for pain is high and the character of the pain is described as sickly meaning of an unusual quality. This quality is illustrated by the peculiar sensibility of the cornea and the glans penis which normally are of similar character. The author can from his own experience with a severed lingual nerve confirm the statement of Trotter and Davis (after O. Foerster⁴²²) that the character of the pain is different from the normal sensation of pain. Only extremes of temperature are recognized in this stage. The temperatures between 24 and 38°C do not cause a sensation of heat. This first stage of the return of the sensibility is called protopathic sensibility.⁴²⁶ It is followed by the return of the sensation of light touch of tactile localization and discrimination as measured by the ability to recognize two compass tips as two distinct points and finally by the restoration of normal sensibility. The second stage of recovery is referred to as epicritic sensibility. Complete restoration of the sensory functions may take up to two years. In skin grafts the sensibility returns after 1 to 12 months and progresses centripetally.

The section of a nerve abolishes the sensory functions in only part of the innervated area. Overlapping of neighboring innervations creates marginal hypoesthetic zones. A persistent circumscribed dermatitis may occasionally follow the section or injury of a nerve. These lesions are restricted to the area supplied.⁴²⁷ They have been used as evidence for a neurogenic theory of eczema.

⁴²²Foerster O. Symptomatologie des Schussverletungen der peripheren Nerven. Berlin 1919 Julius Springer.

⁴²³Lanier L. H. Carney H. M. and Wilson W. H. Cutaneous Innervation Arch. Neurol. 31: 1-60 1935.

⁴²⁴Rothman M. Physiology of Itching. Physiol. Rev. 21: 357-381 1941.

⁴²⁵Head H. Sensibilitätsstörungen. Berlin 1904.

⁴²⁶Herrick R. Dermatitis Following Nerv. Injury Arch. Dermat. & Syph. 26: 879-891 1932.

The sensibility of the skin is considerably influenced by the vegetative system. For example, partial nerve section alone rarely causes circumscribed pruritus or hyperesthesia. This could however be experimentally produced by simultaneous nerve section and sympathectomy.⁶³⁸ Vitiligo and canities have often been observed in the area supplied by peripherally diseased nerves frequently with neuralgia.²¹⁵ This is most often seen in neuralgia of the trigeminal nerve. Zosteriform pigmentations after nerve injury are also known. Paresthesias like numbness or formication give little information about the nature of the nervous lesion.⁶³⁹

Nerve injury, section and central destructive processes may cause *trophic ulcers*. The trophic, i.e. the nutritional balancing influence of the nervous system cannot be denied. The much disputed and not definitely answered question of specific trophic fibers does not seem to be important any longer, since the trophic effects can be sufficiently explained by the known functions of the vegetative system.⁶³⁹ Trophic ulcers are mostly seen on the pressure points of the feet and other sites subject to trauma or infection, e.g. hands, nasal septum and the mouth.⁶⁴⁰ The perforating ulcer has been observed in a great variety of organic lesions, e.g. peripheral nerve injury or therapeutic dissection,⁶⁴⁰ postencephalitic states, tabes, syringomyelia, cervical rib,⁶⁴¹ and others. The ulcer starts as a blister or a sinus underneath a callus. Keratosis of the edge and absence of granulations in the floor are characteristics of the fully developed lesion. The size and course are variable. Keratosis and sinus formation may be excessive, causing deep destruction of bones.

Itching Superficial and Deep Ticking The dermatologically most important neurocutaneous symptom is pruritus. Itching can be elicited by vibrating or constant subthreshold tactile stimulation, i.e. tickling.^{2030, 635, 641} If the stimulus exceeds a certain threshold the normal sensation of pain or touch results and replaces the itching sensation. Scratching relieves itching by replacing it with pain to which itching has many relations.⁶³⁵ Anesthetic areas as a rule do not itch. Intact perception of touch and pain is usually,⁶⁴² but not necessarily, a prerequisite for the eliciting of itching by superficial tickling, i.e. light stroking with a hair or wisp of wool. Thus itching or superficial tickling may still be felt if a hair is lightly run over an analgetic zone in a tabetic, when a needle prick fails to cause pain. In peripheral neuritis tickle is increased where there is intensification to all forms of adequate painful stimuli. In syringomyelia a loss of pain and tickle seem to coincide. With lesions in the *optic thalamus*, there is often intensification of the response to tickling stimuli over the same side of the body on which the responses to painful stimuli are exaggerated. With lesions of the internal capsule and cerebral cortex which have resulted in impairment of sensibility

⁶³⁸ Aubrun E. A. Action vasculaire et action du sympathique dans le prurit par éviction sensitive partielle. *Compt. rend. Soc. de Biol.* 111: 431-48, 1917.

⁶³⁹ Tomma L. Il tema neuro-enlocino ut. *Olo Ital. di dermat. sif.* 373-433, 1934.

⁶⁴⁰ Dalet J. Lésions trophiques de la bouche et des fosses nasales (mal perforant bucconasal des tabétiques) et problème des lésions trophiques. *Ann. de Dermat.* 9: 433, 1937.

⁶⁴¹ Weidman L. Cervical Rib (I skin diseases). *Arch. Dermat. & Syph.* 35: 16, 1937.

⁶⁴² Pritchard F. A. B. The Clinical Significance of Variations in Tick Sensitivity. *Proc. Roy. Soc. Med.* 26: 69, 704, 1933.

neither tickle nor pain sensibility is impaired both are occasionally overactive.⁴¹ This is explained by the assumption that the tickle sensation is conducted by the peripheral neurons to the cord where the pathways cross to the other side in the posterior commissure run through the cord and the medulla near the spinothalamic tract and are finally registered in the optic thalamus not in the cortex.⁴¹ Therefore cortical depressants like morphine paraldehyde and bromine do not influence itching as much as thalamic drugs like phenobarbital.⁴² Section of the interolateral tract of the spinal cord abolishes tickling and itching at the corresponding level while section of the posterior tracts exaggerates these sensations and protopathic pain to which itching is intimately related.⁴³

Drugs which paralyze the sympathetic system like ergotamine tartrate or stimulate the parasympathetic system like yohimbine and muscarine seem to inhibit itching. Königstein⁴⁴ concludes from these observations that the sympathetic system plays a part in the genesis of pruritus. Pruritus seems to be closely connected with dilation of the smaller vessels. It is perhaps a response to changes in the state of permeability.⁴⁵ The psychogenic influence is powerful. This also underlines the importance of the sympathetic factors. Scratching as a prompt reflex reaction to itching is not fully developed before the age of one year⁴⁶ but general reactions may be seen as early as the sixth hour of life. *Deep tickling* is entirely different from superficial tickling and itching though the same word is often used indiscriminately. One should speak of deep tickling when the sensation is felt in deeper structures and when a considerable pressure is necessary to elicit it. Von Rey⁴⁷ relates deep tickling to the sense of pressure superficial tickling to the sense of pain. Tickling is mainly though not exclusively confined to certain areas like the anterior aspect of the neck the armpits the abdomen and the clitoris. A sensation more similar to deep tickling than to itching occurs in the mucosae too e.g. rectum urethra larynx and trachea. A characteristic of deep tickling compared with itching is its relation to uncontrolled reflexes like laughter and other widespread muscular contractions. The crogenic effect of tickling is well known.⁴⁸ Tickling does not elicit scratching but muscular defense.

Head hyperalgesic zones are due to the projection of visceral pain to certain segmental skin regions. These regions correspond to those observed in herpes zoster. Head⁴⁹ mapped such skin zones for many internal organs (see M. Lewandowsky⁵⁰). The validity of the phenomenon has been amply confirmed though there are many controversies over details. It should be emphasized that

Die Welt ist ein Klotz in der Hand der Götter und ein Spielzeug der Menschen. Unten steht die Welt der Menschen. (Zur Festschrift der Universität zu Köln) 1911.

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Head s zones are hyperalgesias. The sensibility to touch is not increased. The diagnosis of Head s zones is made by needle pricks or by slight pinching. Alterations of the sensation caused by tickling with a blunt object have been found to correspond with Head s zones. These zones of decreased, rarely increased sensitivity to tickling are supposed to occur more frequently than the hyperalgetic zones. They indicate the same organ relationship.⁶⁰ A vasomotor reaction to a weak galvanic stimulus can also be used.⁶¹

Herpes zoster of the corresponding region may, though rarely, be the only manifestation of a visceral disease e.g. peptic ulcer, gallstones or cardiac disease.⁶² It is assumed that the viscerocutaneous relation which consists of viscus—sympathicus—intervertebral ganglion—ramus visceralis—gray matter of the spinal cord—anterior root—spinal nerve—skin is affected in the intervertebral ganglion which probably becomes the site of the herpes zoster infection. An interesting visualization of the cutaneous zone corresponding to a lung focus was observed after a weak ultraviolet radiation. Only the skin corresponding to the tuberculus lung focus showed an erythema.⁶³ Circumscribed edema in the viscerocutaneous zones has also been observed.⁶⁴

⁶⁰ Krieger H. Veränderungen des Hitzegefühls der Haut bei Organerkrankungen. Würzburger Abhandlungen vol. 25 No. 6 Leipzig 1930. Curt Kabitzsch.

⁶¹ Kahane M. Die cutane Diagnostik innerer Krankheiten. Wien Arch. f. inn. Med. 36: 110 1911.

⁶² Arnstein A. Herpes zoster als einziges manifestes Symptom von im übrigen latent verlaufende Erkrankungen innerer Organe. Wien klin. Wchnschr. 34 III 14 1921.

CHAPTER XXXVII

DISORDERS OF THE NERVOUS SYSTEM

The Autonomic Nervous System

The autonomic or involuntary nervous system innervates the sweat glands the muscoli arrectores pillorum and the tonus of the blood vessels probably also the secretion of the sebaceous glands. Almost every cell of the skin is surrounded by an extremely fine reticulum of sympathetic fibrils the so-called sympathetic basal plexus or terminal reticulum (Stöhr after F. John²⁶³).

Sweating—The innervation of perspiration has a subcortical center in the hypothalamus. From there the sudomotor impulses descend through the brain stem into the medulla and a series of spinal centers to the anterior roots and the peripheral sympathetic pathways (Walker after Rothman²⁶⁴). A major crossing takes place in the lower pons^{265, 266}. The pathway of the sweat inhibiting action runs through the posterior roots²⁶⁶. In spite of their sympathetic pathway the sudomotor fibers behave like parasympathetic or cholinergic nerves. Their stimulation causes liberation of acetylcholine in the skin and therefore can be suppressed by atropine and enhanced by physostigmine. The formation of acetylcholin in the venous return of a perfused cat leg has been demonstrated with the eserinizied leech preparation²⁶⁷.

Sympathectomy and the section of a peripheral nerve (e.g. the sciatic) causes anhidrosis in the area supplied and hyperhidrosis in the surrounding margin^{268, 269}. A reflexive hyperhidrosis can be observed in the corresponding symmetric zone²⁶⁸. Sweating tests are used in the diagnosis of postural hypotension and in determining the degree of completeness of sympathetic denervation after sympathectomy and removal of sympathetic ganglions²⁶⁶.

²⁶³John F. Skin as Organ Controlled by Vegetative Nervous System. Med. Welt 13: 995-999, 1939.

²⁶⁴Rothman M. Role of Autonomic Nervous System in Skin Diseases. Psychosom. Med. 7: 90-96, 1945.

²⁶⁵Peet M. M. and List C. F. Changes of Sweating in Lesions of Lateral Medulla Oblongata and Upper Cervical Cord. Trans. Am. Neurol. A. 61: 9-15, 1938.

²⁶⁶List C. F. and Peet M. M. Sweat Secretion in Man. Sweating Responses in Normal Persons. Arch. Neurol. & Psychiat. 39: 125-127, 1937.

²⁶⁷Dahl H. H. and Feldberg W. Chemical Transmission of Secretory Impulses to Sweat Gland of Cat. J. Physiol. 82: 1-12, 1933.

²⁶⁸Frölich A. and Zak E. Untersuchungen über die periphere Schweißsekretion. Naunyn-Schmiedeberg's Arch. 166: 620-637, 1933.

²⁶⁹Ackermann A. Studien zur Physiologie der Schweißdrüsen. Dermatologica 79: 219-236, 1939.

²⁷⁰Guttmann L. Motorische und vegetative Grenzonenflexe bei Läsionen peripherer und zentraler Abschnitte des Nervensystems. Z. Neurol. 147: 291-307, 1933.

²⁷¹Brown B. F. Clinical Tests of Function of the Autonomic Nervous System. J. A. M. A. 106: 353-357, 1935.

The spinal centers of perspiration and piloarrection have been mapped and tabulated by Ottfried Foerster⁶³⁰ Central cerebral lesions may cause contralateral hyperhidrosis (*hémiplegie sudorale* Binger and Berg after Marchi⁶³¹ onini⁶³² This however is only marked in early lesions since compensatory mechanisms soon develop and some fibers remain uncrossed Unilateral mostly facial hyperhidrosis is seen in connection with peripheral sympathetic disturbances mostly injuries of the parotid area⁶³⁴ or after thyroidectomy⁶³⁵ Unilateral sweating is often combined with flushing facial paralysis and disturbances of the parotid gland

Ackermann⁶³⁶ found sweat secretion to be the resultant of two antagonistic processes In the proximal section of the gland sweat is secreted through parasympathetic impulses In the more distal part of the tubule a regulating reabsorption under parasympathetic and sympathetic influences may take place⁶³⁸

Our knowledge of the autonomic innervation of the *sebaceous glands* is meager A well known fact is the seborrhea which sometimes follows brain lesions especially of the midbrain and pons (see section on encephalitis)

The psychogalvanic reflex or the Tarchanoff Veraguth phenomenon is the decrease in the *electric resistance of the skin* caused by sensory stimuli and psychic excitement The electric resistance depends on the amount of sweat and is one of the most sensitive psychosomatic reactions Any psychic concentration emotion or effort measurably increases the perspiration The detectors are based in part on the increased sweat secretion under emotion Food ingestion lowers the electric resistance

The reflex may become conditioned so that it occurs at meal time even if no food is being eaten⁶³⁷

The electric resistance is high in areas which do not sweat Therefore the measuring of the electric skin resistance can be used for mapping the sudomotor innervation The areas affected by sympathectomy offer a high resistance to the passage of a very small direct current There may be variations from a few hundred to many thousand ohms within less than $\frac{1}{4}$ inch The electric skin resistance is normally lowest in a sharply demarcated area which includes both eyelids the nose the mouth varying portions of the forehead of the cheeks and of the skin under the lower lip During sleep this area becomes narrowed finally consisting of only a small margin around the mouth Similar areas of low resistance exist on the palms and the soles The patterns of areas of low

⁶³⁰ Marchi I I A Hautkrankeiten und Nervensystem Fortschr d Neurol Psychiat 6 7-25 1934

⁶³¹ Marchi onini A Hautveränderungen bei nichtsyphilitischen organischen Erkrankungen des Zentralnervensystems Fortschr d Neurol Psychiat 6 303-313 1934

⁶³² Rogier H Les syndromes sympathiques d'hémiparésie faciale Riv clin med 24 161-187 1933

⁶³³ L'Herminier J Vasomotorische und trophische Störungen nach Läsion des Halssympathicus II Monatsber f Augenheilk 87 874-885 1931

⁶³⁴ Wilson W C Observations Relating to the Innervation of the Sweat Glands of the Face Clin Sci 2 273-286 1936

⁶³⁵ Regelsberger H Das Electrodermatogramm und die Nahrungsreflexe des Menschen Ergebn d Inn Med u Kinderh 48 125-165 1933

temperatures greater than 3°C justifies immediate amputation of a limb. The level of amputation should not show a temperature lower than 1°C below the corresponding level of the other side.²⁶⁷³ In diabetic gangrene the temperature may be raised; therefore the skin temperature alone is not a reliable indicator for determination of the level of amputation.²⁶⁷³ In arteritis obliterans the feet may be warm. In acute phlebitis the foot temperature is high. The patient should stay in bed until the return of normal temperature.²⁶⁷³ Inflammatory processes increase the skin temperature in a much wider area than the immediate neighborhood of the lesion itself. This seems to indicate that not so much the increased local metabolism but rather the reflex arterial dilation is the cause of the heat in an inflamed area.

There is a rough parallelism between surface temperature especially of the foot and the basal metabolism so that under certain conditions the skin temperature may be used as a substitute or check for the usual basal metabolism test.⁶⁷⁵ High foot temperatures are therefore not only found in hyperthyroidism but also at the end of pregnancy when the basal metabolism is usually increased. These high foot temperatures persist during lactation. In general anesthesia the rise of the foot temperature indicates that the patient is asleep. Primary or secondary sinking of the foot temperature indicates impending or existing shock.²⁶⁵⁰

Morphine Wheal—If the skin is punctured with a needle through a drop of morphine solution a wheal and a surrounding flare appear. Absence of the wheal indicates a block of the small arteries which feed the area as encountered in Buerger's disease. If the peripheral nerve is degenerated the flare may fail to appear.⁶⁸¹

Raynaud's Disease

An invariable association of the peripheral vascular spasms called Raynaud's disease with an internal disorder which might cause the nervous impulses leading to the attack has not been discovered. In fact some analysts^{683, 2684} consider the absence of such a relation as a valuable criterion for the diagnosis of true Raynaud's disease. However the abnormal sympathetic factor which leads to the circulatory changes cannot be denied. Many modern writers on the subject deplore the rather careless labeling of a variety of vascular conditions as Raynaud's disease, Raynaud himself being among the accused.^{2682, 2694} Hunt²⁶²⁵ in an effort to clarify the situation defines Raynaud's phenomenon⁶⁸⁶ as intermittent pallor or cyanosis of the extremities precipitated by exposure to cold without clinical evidence of blockage of the large peripheral vessels and without or not more than skin deep nutritional lesions. However

²⁶⁵ Bierman W. The Temperature of the Skin Surface. *J A M A* 106: 1154-116, 1938.

²⁶⁶ Haxthausen H. Morphine Puncture: A Method for Diagnosing Affections in the Peripheral Arteries and Nerves. *Acta dermat. venereol.* 20: 508-513, 1939.

²⁶⁸² Raynaud A. G. M. De l'asphyxie locale et de la gangrène symétrique des extrémités. *Thèse de Paris*, 1862.

² Allen E. V. and Brown G. E. Raynaud's Disease (147 Cases). *J A M A* 111: 147-1478, 1932.

²⁶⁸⁴ Allen E. V. and Brown G. E. Raynaud's Disease: Diagnosis. *Am J M Sc* 133: 187-200.

²⁶⁹⁴ Hunt J. B. Raynaud Phenomena. *Quart J Med* 5: 399-444, 1936.

³ Lewis Th. and Pickering G. W. Raynaud Disease. *Heart* 13: 7306, 1934.

the time honored term Raynaud's disease defies eradication. If one keeps Hunt's definition in mind there is no reason to abolish it since the term disease is often used for a syndrome or phenomenon of unknown cause.

In the attack the skin of the fingers less often and less severe than of the toes becomes suddenly pale and cool often painful. The skin temperature may be lowered as much as 16.7 centigrades (30 fahrenheit degrees). The volume of the involved part is decreased. In this stage a needle prick does not cause bleeding. Cyanosis (local asphyxia) predominates in severer cases and may produce a blue, brown slate or even black color. The skin becomes white on pressure but is extremely slow in taking on the color of the surrounding area after the pressure has been released. The radial pulse remains perceptible during the attack. The attack ends with a change of the color to vivid red caused by a violent reactive hyperemia. The changes are symmetrical. The sensibility is often disturbed but not abolished and the disturbances of sensitivity are like the pain ill defined and not limited to the area supplied by one nerve. Anhidrosis or hyperhidrosis occurs. Only in severe cases do trophic lesions like shallow ulcers, paronychias and atrophy of the nails, muscles and bones become apparent. In later stages the finger tips may be covered with a great number of small depressed scars. If gangrene occurs, it is usually superficial and always dry. Hardly ever do areas larger than an end phalanx become necrotic.

The attack can be precipitated in many cases by immersion of the hand in cold water or by exposure to cool air or by chilling of the body by cold drinks.⁸⁸⁷ Cold is the most important immediate cause although emotion also plays an important part in the precipitation of the attacks.^{888 2022 889} The trouble is predominantly found in young and middle aged women. The prognosis is usually good with respect to life but the attacks may recur over many years. The pathogenesis of the phenomenon is still controversial. Raynaud and many others after him believed that an abnormal vasomotor tone was the main pathogenetic factor. Lewis (see Hunt⁸⁸⁹) produced much physiological evidence to the effect that the vasomotor tone was in order but that there was a local fault in the medium sized digital arteries.²⁰⁰⁰ Several autopsies on cases having had the disease for long periods of time have not revealed any changes in the arteries^{981 89} but a few instances of endarteritic alterations have been observed (Kolisch after Mucha²⁰⁰³). Microscopic changes in the sympathetic ganglia and other nervous centers are on record.⁸⁹⁴ The vascular as well as the neural findings are not uniform and some are probably secondary. The capillaroscopic picture during the attack is characterized by the empty and seemingly absent

⁸⁸⁷Johnson C A Raynaud's Disease 2 Cases Surg Gynec & Obst 72 889 907 1941

⁸⁸⁸Craig J B Raynaud's Disease Psychogenesis Dis Nerv System 5 14 146 1944

⁸⁸⁹Mufson J Raynaud's Disease Ann. Int. Med 20 28 938 1944

⁸⁹⁰Hyndman O R and Wolke J Raynaud Disease Vascular—not Sympathetic—Disease Am Heart J 23 535-554 1942

⁸⁹¹Dannigeb H Ein Fall von Raynaud'scher Krankheit mit Obductionsbefund Diss. Freiburg 1933

⁸⁹²Lerich R and Fontaine R Sur la nature de la maladie de Raynaud Pres. med. 1937 II 19 1 19 5

²⁰⁰⁰Mucha V Die Raynaud'sche Krankheit Hb. d. f. H. u. Gk. 2 273-300 19 8

²⁰⁰³Pallasse Dechaume J and Arnaud Lésions de la chaîne sympathique dans la maladie de Raynaud Lyon méd. 1931 II 117 124 Zbl. 40 71

capillaries and the constricted arteries. The spastic picture is followed by tonic dilatation in the asphyctic stage but both spasm and atonia may be seen simultaneously.¹⁷⁰ The capillaroscopic changes exceed the macroscopically changed areas. There can be no doubt that vasomotor stimuli play an important part. This is best demonstrated by the immediate success of surgical removal of the sympathetic fibers or ganglia through which the vasomotor stimuli must pass. After sufficiently extensive sympathectomy by one of the many suggested methods (Review and Methods see Homans¹¹¹ and Adson¹⁰⁹) the vascular paralysis which follows the operation leaves the fingers flushed and no attacks occur as long as the sympathetic fibers do not regenerate.

The associated conditions which can be found in patients with Raynaud's disease are most often of functional character. In 24 per cent of a series of 147 noncomplicated cases psychoneurosis or neurasthenia was obviously a feature.¹⁰⁴ Syphilis, arteriosclerosis and a number of rare diseases¹⁰⁵ have been found in connection with Raynaud's syndrome. Linenthal¹⁰⁶ described 5 cases with pulmonary fibrosis. A rare finding is a cervical rib. If this anomaly is unilateral the attacks are unilateral but intermittent in spite of the continuous cause.^{111, 106, 107} Menopause^{109, 1701} sclerodactyls,^{106, 170} arsenical¹⁰³ and copper poisoning⁷⁰² are other rare combinations. Lewis and Landis¹⁷⁰⁴ make use of the combination with sclerodactyls to support the arteritic theory of Raynaud's disease. Scler¹⁷⁰³ separates sclerodactyls (acroscclerosis) from Raynaud's disease as well as from scleroderma. Combination with tetany,⁷⁰⁶ and calcifications^{70, 1708} have caused speculation about a parathyroid etiology. Subtotal parathyroidectomy has not proved successful.¹⁰⁰

Treatment—Since the paralytic hyperemia does not last the enthusiasm about the surgical approach has somewhat abated so that lately medical management has again been said to give equally satisfactory results. Johnson¹⁰⁷ stresses prevention of attacks by avoiding the thing that precipitates them.

¹⁰⁹Adson A W. Raynaud's Disease. Results of Sympathectomy. 8 Clin North America 17 1061 1937.

¹⁰⁶Linenthal H. Raynaud's Disease. Pulmonary Fibrosis. 2 Cases. New England J Med 227 433 436 1942.

¹⁰⁷Dequé J and Lelong M. Côte ce vicale bilatérale. Syndrome de Raynaud unilateral. Bull et mém Soc nat de chir 11 1073 1063 1935. Zbl 52 464.

¹⁰⁸Casali er H. Vasomotorisch trophisch. Neurosen ed 2 Berlin 10 2 S. Targier.

¹⁰⁹W. th. Raynaud'sche Krankheit und Eritaria chronica papulosa. Zbl 14 20 19 4.

¹¹⁰Borneo A. Raynaud's Disease in Menopause. W. n med Wchschr 75 170 71 19 5.

¹¹¹Becker G. Die Lösung d. Hände im Klimakterium. Zbl 46 577 1930.

¹⁷⁰Barton R G and Loppel W H. Raynaud's Disease Int. stitital Calcinos Circumscripta. Associat d With Scleroderma. Radiology 29 96 98 194.

¹⁷¹Simon A. Leber I. upferschädigungen und die Beziehung zum Raynaudschen Symptomen. Kompl. x. Ar. d. f. Gew. rb. path. 2 71 80 1931. Zbl 38 504.

¹⁷²Lewis T and Landis E M. Raynaud's Disease. Sp. cial R. f. ceases to Arteriole Defects and Scleroderma. Heart 15 379 380 1931.

¹⁷³Sellef J. Akrosklerose und Raynaudsche Krankheit. Arch. f. Dermat. u. Syph. 173 35 356 1936.

¹⁷⁴Borowsky M L. Die Pathogenese der Raynaud'schen Krankheit. Deut. che Ztschr. f. Nervenh. 114 232 254 1930.

¹⁷⁵Rhee G van. Raynaud's Disease With Calcareous Deposits. Arch. Dermat. & Syph. 29 930 1934.

¹⁷⁶Walker R H. Calcification in Raynaud's Disease. Proc. Roy. Soc. Med. 27 6 7 628 1934.

Secondary anemia should be treated. Pancreatic extracts and thyroid²⁷⁰⁹ have been advocated. Paraffin baths also have given considerable relief. The attack is best treated by immersion of the hands into warm not hot water.

Erythromelalgia (Weir Mitchell's Disease)—This syndrome features attacks of severe pain, redness and swelling usually of the feet. Hyperhidrosis is usually present in the involved area. The paroxysms are sometimes precipitated by exposure to warmth and depression of the limb. Though occasionally associated with Raynaud's disease, it exhibits in many respects the opposite phenomena. Among a great number of occasional associations the connections with polycythemia (see there), Bence Jones albuminuria and neurasthenia must be mentioned. 18 163 710 11

Acrodynia (Feer's Disease, Pink Disease)

Acrodynia though probably known and described in France under this name^{2713 714} more than a century ago has become better understood and more sharply defined only during the present century. The names of Swift²⁷¹⁵ Selter⁷¹⁶ and particularly Feer²⁷¹⁷ after whom the disease is often named designate some of the many authors who have been concerned with it.

The disease affects small children almost exclusively. According to Feer²⁷¹⁷ the onset is insidious. The children are listless irritable sometimes vicious and do not care to play. The facial expression is frowning unchildlike weary so that the experienced physician can make the diagnosis on the physiognomy alone especially if the contracted eyelids are added to the picture. The sleep is disturbed and the appetite lost. Fatigue and gradually developing motor disturbances like unwillingness or inability to walk or stand a bizarre and persistent jackknife like position in bed with the head between the feet general flaccidity of the muscles without atrophy frequent light tremor and other nervous symptoms are essential features. Other important signs are increased pulse rate and blood pressure high basal metabolism high blood sugar and high sedimentation rate. The temperature may be normal but fever has often been observed in the beginning and during complications. Monothermia is sometimes a remarkable feature. Encephalitic features resembling parkinsonism have been observed.²⁷¹⁸

²⁷⁰⁹ Ipsen J. Zwei Fälle von der Raynaudschen Krankheit mit Untersuchungen der Arterien. Acta chir Scandinav 71 49-49 193. Zbl 45 474.

²⁷¹⁰ Hirschfeld H. Erythromelalgie. Handb d H u Gk 6 60-73 193.

²⁷¹¹ Lewis Th. Clinical Observations and Experiments Relating to Burning Pain in the Extremities and to so-called Erythromelalgia. Clin 9c 1 175 211 1933.

²⁷¹² Brown G. Erythromelalgia and Other Disturbances of the Extremities Accompanied by Vasodilatation and Burning. Am J M Sc 82 469-495 1937.

²⁷¹³ Chardon. De l'acrodynie ou épilemie qui a régné à Paris il y a 180 ans. Rev méd franç et étrang 3 51 1830.

²⁷¹⁴ Pichu M. Acrodynie d'autrefois et acrodynie d'aujourd'hui. Bull Acad d m d Paris 111 111 547 553 1934.

²⁷¹⁵ Swift H. Erythroedema. Lancet 1 611 1919. (Letter to the editor.)

²⁷¹⁶ Selter J. Acrodynia. 42 Cases. Arch f Kinderh 80 44 5 1917.

²⁷¹⁷ Feer E. Acrodynia. In Picturae et Tractatus of Pfäundler and Schlossman. The Diseases of Children. Vol III. Philadelphia 1935. J B Lippincott Co. pp 423-445.

²⁷¹⁸ Morquio L. Ueber ein neues Kindersyndrom Akrodynie. Arch de pédiat d Uruguay 2 10. 118 1932. Zbl 43 58.

Acrodynia takes a protracted course over many months. Complete recovery is the rule. Recurrences are rare.²⁷¹⁹ The mortality rate among 200 cases in Australia was 3 per cent²⁷²⁰ when the patients were treated in their own homes but rose to 30 per cent under hospital care with the danger of intercurrent infection. Higher mortality rates have also been observed.^{2717, 2718, 2721}

Dermadromes—Dermadromes occur frequently²⁷²² and may at times completely dominate the picture. From the start the skin feels cold clammy and flabby. *Sweating* to a degree which has its equal only in miliary fever weakens the patient and causes thirst. Sparse or copious miliaria rubra²⁷²³ or micro papular follicular eruptions soon follow the excessive sweating. The skin between the miliary papules may be diffusely bluish or red, the texture from which the

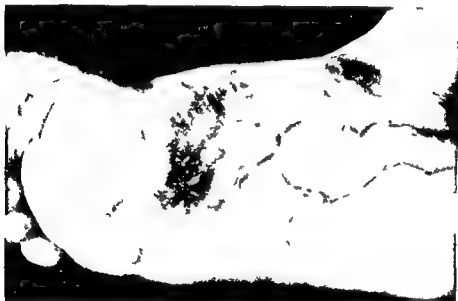


Fig 241—Acrodynia. Left leg (Patient of Dr G. F. Kohn.)

name pink disease was derived (Glubbe after Crawford²⁷²⁴). The papules may enlarge and become scaly and eczema like. Cases of acrodynia have often been mistaken for eczema as long as the other important symptoms had been overlooked. In typical cases of acrodynia the macerated skin soon peels in large

²⁷¹⁹ Péhu M. Recidivations of Infantile Acrodynia. *Schweiz med Wchnschr* 71: 1207-1208, 1941.

²⁷²⁰ Wood A. J. and Wood J. Pink Disease. *Brit M J* 3898: 527-531, 1935.

²⁷²¹ Ratcliffe T. A. Acrodynia. *J Ment Sc* 87: 545-571, 1941.

²⁷²² Bode H. Die Feersche Krankheit im Licht der Dermatologi. *Arch f Derm u Syph* 187: 15-46, 1932.

²⁷²³ Gooster H. R. Erythredema Polynuritis. *Arch Dermat & Syph* 11: 173, 1925.

²⁷²⁴ Crawford G. Juvenile Acrodynia. Eleven Cases. *Arch Dermat & Syph* 26: 215-37, 1932.

²⁷²⁵ Audeoud H. and Boissonas L. 18 Cases of Acrodynia. *Rev méd de H Suisse Rom* 59: 785-794, 1939.

²⁷²⁶ Feßler A. Hautveränderungen bei der Feerschen kindlichen vegetativen Neurose (Selter Swift Feersche Krankheit). *Arch f Dermat u Syph* 173: 290, 1935.

flakes or in smaller circular patches. The *peeling* is particularly marked on the hands and feet so that it may be mistaken for scarlatina. Besides rashes from sweating, and repeated crops of macular urticarial or multiform exanthems may occur especially on the mesial areas of the trunk²⁷⁰ sometimes also on the extremities. Itching is most violent. Scratching and possibly trophic disturbances may cause pyodermic ulcerative and necrotic complications. Bed sores occur quite frequently. The teeth may become loose and fall out. Geographic tongue is a frequent feature²⁷¹⁷. Salivation frequently adds to the discomfort, and may outlast the excessive perspiration. The hands and feet show a characteristic purplish pink erythema. The nose and cheeks may also be red.

The *hair* becomes dull and is often shed. The young patients often like to pull the loose hair out and the vertex frequently becomes bald.

Diffuse and focal inflammatory changes have been found in the sympathetic system so that the disease has been explained as a disorder of the vegetative nervous system and the term *pansymphilitis* used⁷¹⁷ 7 731.

The nature of the anatomical changes in the cerebrospinal system are still controversial⁷² 734. Several neurologists believe that encephalitis influencing the vegetative centers of the *thalamencephalon* plays a part. In the skin hyperkeratosis parakeratosis intracellular edema⁷³⁴ and inflammatory infiltrations in the stratum subpapillare with damage or loss of the elastic fibers and vaso dilatation are microscopic features. Bode²⁷²⁸ described eosinophile bodies in the prickle cell layer surrounded by lamellated cells.

The disease is probably an infection of the autonomic nervous system though neither microbes nor positive animal inoculations have been demonstrated. However local accumulations of cases a few familial cases²⁷²⁶ 2727 the seasonal increase in winter and spring and the existence of fever inflammation and apparent but not invariable immunity after recovery make the infectious etiology attractive. Endocrine²⁷²⁸ toxic avitaminotic or chronic neurotrophic⁷²⁹ hypotheses have been suggested. An interesting argument in favor of the in

²⁷¹⁷ Péhu M, Dechaum J and Boucomont J. L'acrodynie infantile. Anatomie pathologique. Bull Acad de méd Paris III s 113 818 923 1935.

²⁷²⁸ Péhu M and Boucomont J. L'acrodynie infantile. Atti 15 Congr Ital Pediatr pp 557 548 1934. Zbl 52 2.

²⁷²⁹ Péhu M, Dechaum J and Boucomont J. Sur l'acrodynie infantile. Rev franç de pédiat 12 39 2 6 777 310 549-607 936. Zbl 54 333.

⁷² ou l'equand G Dechaum J and Sedallan P. Tentatives d'expérimentation sur l'acrodynie encephalite spontané du lapin. Ann de méd 41 85 99 1937.

⁷³⁴ Clément R. Formes atypique de l'acrodynie. Pre méd II 1607 1610 1935.

²⁷²⁶ Wolf I J and Davison Ch. Acrodynia. J Pediat 4 499-506 1931.

²⁷²⁷ Deam r W C and Biskind G R. Acrodynia. Am J Dis Child 48 13 6-1335 1934.

²⁷²⁸ Bellocq H Ph and Mey R. Étude Clinique et Anatomopathologique d'une Forme grave d'acrodynie. Rev franç de pédiat 8 495-503 1932.

²⁷²⁹ Blechmann H, Montlaur H and Leconte A. L'acrodynie maladie contagieuse? Présentation de deux frères acrodyniques. Bull Soc de pédiat de Paris 31 135 137 1933.

²⁷³⁰ Blechmann G and Leconte A. Acrodynie familiale (Trois enfants). Bull Soc de pédiat de Paris III 5 0-6 3 1 1935.

⁷²³ Rietschel H. Zur Pathogenese der Feerschen Krankheit. Deutsche med Wch schr 191 I 723 725.

²⁷² Bode H C and Schreuff A. Feersche Krankheit. Zbl 43 751 750 1932 1933.

fectious etiology is the epidemiological and clinical relationship to acute miliary fever which has similar geographic distribution and symptomatology. Its course, however, is much more acute and dangerous.

No specific treatment has been found. Feer advocates high doses (2 mg daily) of atropine. Ultraviolet light has also been found effective.

CHAPTER XXXVIII

DISORDERS OF THE NERVOUS SYSTEM

Neurocutaneous Diseases

The common ectodermal origin of essential parts of the skin and the nervous system is reflected in some diseases which affect both systems at the same time and in the same or at least in a comparable manner. These diseases have been called neurocutaneous diseases or congenital ectodermoses. The group comprises von Recklinghausen's disease (neurofibromatosis), Bourneville's disease (tuberous sclerosis of the brain) and various types of angiomatosis of the brain, eye and skin.

Von Recklinghausen's Disease—Von Recklinghausen's disease is because of its frequency by far the most important member of the group. The dermadromes, tumors and pigmentations are the most common and striking manifestations of the disorder. The tumors may appear as fibromas and neurinomas which cannot always be distinguished clinically. Particularly the nature of small tumors may be doubtful. In large soft fibromas a wormlike, neuroinomatous plexus may be palpable indicating the ill defined clinical borderline between the two types of lesions.

The *fibromas* are usually soft (*fibromata mollusca*) and indolent, rarely firm. They may vary in number from a few to several thousand. There does not seem to be any site of predilection although the large fibromas seem to arise more often on the eyelids, the buttocks and the labia majora. The tumors may range from pinhead sized nodules to gigantic growths weighing more than 80 pounds. If such large tumors involve an extremity the term *elephantiasis mollis* is often used. The fibromas may be flush to or raised above the level of the skin and the base may be thin or wide, the tumor accordingly appearing pedunculated or sessile. The covering skin is most often normal in appearance but sometimes it is pigmented, leathery and warty. A peculiar type is represented by fibromas which give the appearance of an empty bag of scrotum like wrinkled soft thick skin (*pachydermatoceles*). Such flabby tumor formations may be seen on any part of the body surface. Trauma may change them into large and troublesome hematomas. The surface of the fibromas may show comedos or local hypertrichosis. The palms and soles are seldom involved. Spontaneous involution is very rare.²⁷⁴⁰

The *neurinomas* (neurofibromas) represent the second type of Von Recklinghausen neoplasms. In typical instances they are much firmer than the fibromas and tender on palpation or sometimes spontaneously painful. They are often spindle shaped or show their neurogenic origin by palpable worm or

²⁷⁴⁰ *See also* H. E. and *See also* H. L. : *Hautmyome Recklinghausens et Hautbaldhru Gk* 12, 2 55 191 193

plexus like structures. The neurinomas may develop anywhere along peripheral nerves or in the central nervous system and they too may reach very large sizes.

In one of the cases presented by Jones Jr. and Hart²⁷¹ the mass grew slowly from a small buttock tumor to a size which exceeded half of the entire body of the 36 year old emaciated man.



Fig. 342.—Von Recklinghausen's disease.

The *pigmentary* lesions of Von Recklinghausen's disease occur as large and small spots. H. W. Siemens²⁷² emphasizes that the large spots differ from the ordinary smooth pigmented nevi. Their edges are smooth and their color is yellowish brown while the true nevi spots have a more jagged contour and an olive shade. The large Recklinghausen spots range from fingernail to palm size the larger ones often being oval shaped and arranged in the direction of the cutaneous lines of cleavage. Their color is best characterized by the often used term *café au lait*. The small spots resemble freckles but their distribution is even and

²⁷¹Jones R. Jr. and Hart D. Multiple Neurofibromatosis. *Ann. Surg.* 110: 916-939, 1939.

²⁷²Siemens H. W. Clinical and Dermatologic Studies on Recklinghausen's Disease. *Arch. f. Dermat. u. Syph.* 160: 80-103, 1926.



Fig 343 — Von Recklinghausen's disease



Fig 344 — Von Recklinghausen's disease — Empty pocket (From Hart — Ann Surg)

is not influenced by exposure to light²⁷⁰² The small spots may be innumerable Pigmented spots of both kinds are hardly ever missed They may precede other skin manifestations by many years Ordinary and unusual nevi e.g. the so called bathing trunk nevus hemangiomas and the nevus anaemicus have been noticed in a number of instances^{2701 703}

The systemic character of Von Recklinghausen's disease manifests itself in the multiplicity of organic involvements Abdominal intestinal⁷⁰⁴ intra



Fig 31 —Von Recklinghausen's disease Giant fibroma of the face with pseudo-cystic lesion



Fig 31b —Von Recklinghausen's disease Empty pouch

²⁷⁰²Wakel y C. B. G. and W. ber F. P. Generalized Neurofibromatosis With Naevus Anaemicus Internat Clin 18 r 46 144 147 1936

⁷⁰³Barton A. B. and Inglis J. Neurofibromatosis With Both Cutaneous and Visceral Lesions J Coll Surg Australasia 9 397-40 1931 Zbl 39 55

pleural⁷⁴⁵ and mediastinal⁷⁴⁶ neurofibromas as well as sciatic nerve tumors illustrate some of the many rare localizations. Of greater importance are the neurinomas of the central nervous system and of the intracranial nerves. A considerable part of the meningiomas of the tumors of the spinal cord of the cerebello pontine angle and of the acoustic nerve belong here.^{830 274 51}

The symptomatology of these central tumors depends on their location. The central neurinomas are usually not malignant although their site may make them extremely dangerous.

Perhaps of greater practical importance than the relatively rare central lesions are the involvements of the skeleton. Here too the site is more im-



Fig. 317.—Von Recklinghausen's disease. Enormous neurofibroma of the hip. (From Hart, *Ann Surg*.)

portant than the size or number of the lesions which cause cystic destruction and peculiar irregularities in the growth of some long bones as a sequel to epiphyseal or shaft lesions during the growing age.²⁷¹ Kyphosis may be an early symptom even before skin lesions are noted. Kyphoscoliosis has been observed

⁷⁴⁵Castiglioni T. Die Intrathorakalen Neurofibrom. *Röntgenprax* 3: 14-19, 1931.

⁷⁴⁶Mahaim H, Henthorpe J O and Allbach H K. Neurofibromatosis With Malignant Thoracic Tumor and Metastasis in a Child. *Am. J. Dis. Child* 57: 391-399, 1939.

⁸³⁰Antonini R F. Rückenmarkstumoren und Neurofibrom. *Anatomie und Embryogenese*. München und Wienbaden 1909. J. P. H. Hermann.

²⁷¹Mosbacher F W. Recklinghausensche Krankheit und Tumore cerebraler Psychiatrie. *Neurol. Wchnschr.* 1931 II: 411-418.

²⁷⁴Mosbacher F W. Recklinghausensche Krankheit. *Fortsch. d. Neurol. Psychiat.* 3: 229, 1931.

⁵¹Hilmoortel J Jr and Thiepont R. Tumeurs bilatérales de l'acoustique dans la neurofibromatose. *J. belge de neurol. et de psychiatrie* 33: 79-745, 1933.

⁵¹Foerster H and Gell O. Zentral diffuse Schwannose bei Recklinghausenscher Krankheit. *Z. Neurol.* 151: 116, 1934.

in as many as 43 per cent of some series²⁷⁵ Pseudarthroses of the legs cystic destruction of the hip bones^{275a} compression of the spinal cord^{275a} and osteomalacia^{275a} represent some of the typical skeletal phenomena Moderate acromegaly^{275a} cutis verticis gyrata²⁷⁵⁷ Frohlich's syndrome^{2758 2759} adrenal symptoms²⁷⁶⁰ vagus tumor²⁷⁶ high blood calcium and potassium²⁷⁶³ and many other endocrine features²⁷⁶ have been recorded without leading to a well founded endocrine theory of the pathogenesis of Von Recklinghausen's disease²⁷⁶¹ In this connection the unfavorable influence of puberty and pregnancy on the production of tumors must be mentioned Psychic anomalies including all degrees



Fig 348 — Von Recklinghausen's disease. Large and small pigmented spots

- ²⁷⁵²Stalman A. Nerven Haut und Knochenveränderungen bei der Neurofibromatosis Recklinghausen. Virchow's Arch f Path Anat 289 96-126 1933
- ²⁷⁵³Richter W. Neurofibromatosis Recklinghausen mit cystischen Veränderungen in den Hüftgelenkknochen. Zbl 11 37
- ²⁷⁵⁴Mittler A. Neurofibromatosis With Reference to Skeletal Changes Compression Myelitis and Malignant Degeneration. Arch Surg 22 109 122 1936
- ²⁷⁵⁵Cole H. N. and Driver J. R. Von Recklinghausen's Disease. Arch Dermat & Syph 22 753 1930
- ²⁷⁵⁶Blotvogel H. Die Charakterbildung der Neurofibromatose (Recklinghausen). Dermat Wechnschr 1933 I 301 309
- ²⁷⁵⁷Rajka M. Pachydermie vocis (Cutis verticis gyrata). Morbus Recklinghausen. Zbl 11 15 1933
- ²⁷⁵⁸Rusakova B. Zur Frage der endokrinen Anomalien bei der Recklinghausenschen Krankheit. Russk Vest Dermat 2 1931 Zbl 39 315
- ²⁷⁵⁹Obstánde E. Zur Frage der Dystrophia pluriglandularis neurofibromatosa. Wien med Wechnschr 1931 I 638 639
- ²⁷⁶⁰Roseenthal H. B. and Willis R. A. Association of Chromaffin Tumours With Neurofibromatosis. J Path & Bact 42 599 603 1936
- ²⁷⁶¹Levin O. L. and Behrman H. T. Neurofibromatosis—Elusive Manifestations and Internal Relations. Arch Dermat & Syph 41 490-50 1940
- ²⁷⁶²Siebnér M. Vagustumor bei Recklinghausenscher Neurofibromatose. Deutsche Ztschr f Chir 237 63 79 1932
- ²⁷⁶³Mariante Th. and Maciel P. Recklinghausen's Disease and Ca Metabolism. Rev radiol o clin 1 332 341 1932 Zbl 11 533
- ²⁷⁶⁴Freund H. Über endokrine Störungen bei Recklinghausenscher Krankheit. Arch f Dermat u Syph 168 128 142 19 9

of feeble mindedness and frank psychosis ^{75 765 2767} are common Hebra believed "that all patients suffering from fibroma molluscum were mentally retarded individuals" In a modern series ⁷⁴⁸ about one half of the patients showed mental deficiencies

The patients afflicted with Von Recklinghausen's disease often have a characteristic melancholic or bored facial expression which Rille ⁷⁶⁸ partly ascribes to changes in the facial skin The eyes and ears participate in the morbid process in many ways There may be enormous tumors of the lids^{2 69} and of the



Fig 349 --Von Recklinghausen's disease Small pigmented spot and larger pigmented moles The patient is only 2 years old the mole is mostly small and not too numerous (Courtesy Wisconsin Memorial Hospital)

⁷⁷⁴Hubble D and Rogerson C H Anxiety Alopecia Areata Neurofibromatosis Auricular Fibrillation Case Br J J 1 486-488 1941

⁷⁷⁶Sostakovic V Symptomatologie der Recklinghausen'schen Krankheit Obozr P'shiatr 4 167 173 1929 Zbl 36 77

⁷⁷⁷Woringer F Maladie de Recklinghausen Bull Soc franç de dermat et yph III 1510 1512 1932

⁷⁷⁸Rille Der ist nicht ausser dem Gesichtes kann ich den Morbus Recklinghausen Dermat Wchns hr 1935 II 143-145

⁷⁷⁹Knapp A A Von Recklinghausen's Disease Case With Involvement of Left Eyelids J A M A 100 494-495 1933

sclerotic²⁷⁷⁰ buphthalmos changes of the retina and of the optic nerves or their surroundings,²⁷⁷¹ and tumors²⁷⁷²

Deafness from bilateral acoustic nerve tumors and other nervous disturbances of hearing are well known and sometimes demonstrable by roentgenographic examination of the petrous bone^{2773 2774}

The disease is hereditary though certain factors may be necessary to make the hereditary character manifest. The trouble has been seen as a concordant feature in homozygotic twins^{7 6 2775 2776} occurring in six generations²⁷⁷⁷ and in as many as four siblings²⁷⁷⁸. Among 115 children of Recklinghausen patients 43.5 per cent were afflicted²⁷⁷⁹. H. W. Siemens characterizes the inheritance of Recklinghausen's disease as an irregularly dominant one. Solitary cases without apparent familial connection are not rare. Both sexes are equally affected²⁷⁸⁰. The tendency to malignant degeneration of Recklinghausen tumors may be familial (Hockstra after Mosbrucher⁴⁹).

The syndrome occurs in many degrees of severity. Within one family cases with all types of manifestations may be seen together with cases whose only symptoms may consist of some pigmented spots without tumors. Generally the term *formes frustes* is applied to cases with less than the four types of dermadromes: the large and small pigmented spots, the fibromas and the neuromas. Apparently abortive cases showing very few lesions may still become severe²⁷⁷⁸.

The disease may be congenital but commonly comes on gradually²⁷⁷⁸. At certain periods however like puberty, pregnancy and the menopause and after infections like typhoid and mumps the rate of appearance of new symptoms may be stepped up. Since the lesions only come and do not go older patients usually have more than younger patients.

The course of the disease has already been indicated. In advanced age, the cases often become more progressive and changeable^{2 40}.

The life expectancy is generally favorable but may be entirely changed by complications particularly of the nervous and skeletal systems. Sarcomatous degenerations of (see Charache²⁸¹) tumors occurs in about 10 per cent⁷¹⁰ prob

²⁷⁷⁰Mamoli L. Caso di morbo di Recklinghausen con manifestazioni endocraniche e rara localizzazione epilobare. Atti Congr. Oftalm. pp. 663-65. 1932. Zbl. 66. 64.

²⁷⁷¹Webe F. I. and Hode O. B. Recklinghausen's Neurofibromatosis With Unilateral Buphthalmos and Multiple Chasms in the Face. J. Skull Pro. Roy. Soc. Med. 27. 638-640. 1934.

²⁷⁷²Gardner W. J. and Turner O. Bilateral Acoustic Neurofibromas. Arch. Neurol. & Psychiat. 70. 92. 1940.

²⁷⁷³H. Uebelin G. W. Peniergras F. I. and Widmann B. P. Roentgenographic Findings in Neurocutaneous Syndromes. Radiology 35. 617-7. 1940.

²⁷⁷⁴Leis H. H. Klinghaus's Krankheit und cerebrales Syndrom bei einem einzigen Zwilling. paar. Ztschr. f. m. ch. u. verb. u. Konstitutionskr. 19. 7. 1. 1936.

²⁷⁷⁵Lofitis E. L. Neurofibromatosis in Identical Twins. Arch. Dermat. & Syph. 42. 657. 1940.

²⁷⁷⁶Landau A. 4 Brothers With Neurofibromatosis. Brit. M. J. 2. 190. 1941.

²⁷⁷⁷Freiser A. A. and Davaport C. B. Multiple Neurofibromatosis and Its Inheritance. Am. J. M. Sc. 156. 507-540. 1919.

²⁷⁷⁸Gaté J. and Cullier E. L. In cas de maladie de Recklinghausen. Bull. Soc. franc. dermat. Syph. 40. 3-5. 1933.

²⁷⁷⁹Andruss G. C. Von Recklinghausen's Disease. Arch. Dermat. & Syph. 24. 685-688. 1931.

²⁷⁸⁰Sharpe J. C. and Young H. H. Recklinghausen's Neurofibromatosis. 31 Cases. Arch. Int. Med. 59. 299. 1933.

²⁷⁸¹Charache H. Multiple Neurofibroma With Sarcomatous Transformation and Skeletal Involvement. Arch. Dermat. & Syph. 40. 185-191. 1939.

ably even less frequently. The patient dies with Von Recklinghausen's disease but rarely of it.¹⁷⁸

The microscopic structure of the neurinomas shows bandlike zones of parallel elongated nuclei alternating with zones of parallel thin fibers without nuclei. Sometimes the fibrous part is transformed into a dense finely reticular structure with fusiform and anastomosing cells. Mitoses are very rare. The growth generally has all the characteristics of a benign neoplasm. Most pathologists believe that the neurinoma stems from the cells of the sheath of Schwann thus being of ectodermal origin. The theory of mesodermal nature is defended by a minority, an important argument being the transition into sarcomas.^{782, 278b}

No satisfactory method of treatment is known.

Many authors advise against inadequate surgical removal of tumors because of the danger of sarcomatous degeneration.⁶⁶⁷ The removal of one sarcomatous growth may be followed by a distantly located sarcomatous transformation.⁷⁸¹

Tuberous Sclerosis of the Brain—(Bourneville's Disease). This is a congenital, progressive and often familial condition. It is characterized by epileptic seizures of varying types, mental deficiency, varying from queerness or feeble mindedness to severe idiocy, by eye disorders and dermadromes. The triad of adenoma sebaceum, epilepsy, and mental deficiency is called epiloia. The brain lesions are whitish, relatively firm, well circumscribed plaques and tumors. They are found in varying parts of the cortex as well as in the ventricles. In the lesions the nerve cells are widely destroyed or damaged by neuroglial proliferation and other processes among which a certain type of large cell and a tendency to calcification are prominent features. The latter and frequent hydrocephalus are radiographically demonstrable.⁷⁷² Tumors resembling hypernephromas, rhabdomyomas of the heart and a variety of other neoplasms may be found. A high basal metabolism,⁷⁸⁶ gynecomastia, precocious puberty,⁷⁸⁷ congenital malformations,^{2788, 2789} and neurogenic mulberry shaped tumors of the retina⁷⁹⁰ have been described in association with tuberous sclerosis. The disease becomes manifest in early childhood and runs a slowly progressive course. The majority of the patients die before the age of 25 years (Bielschowsky and Gallus after E. Guttman²⁰³⁰).

¹⁷⁸Harbitz P. Multiple Neurofibromatosis. *Arch Int Med* 23:6, 1909.

⁷⁸²Cushing H. and Eisendrath L. *Neurolinguias* Springfield Ill. 1933. Charles C. Thomas.

⁷⁸¹Orechowski K. *Neurodermatology* Handb. d. H. u. Gk. 12, 1937.

⁷⁸⁰McNairy D. J. and McTigue J. H. Cutaneous Tumors of von Recklinghausen Disease.

Arch Dermatol Syph 61:344-390, 1945.

⁷⁸⁶Kreyenbrock G. Delbanco E. and Haach F. Tuberoses Sklerose und Adenoma sebaceum.

J. Neur. 128:236-56, 1930.

⁷⁸⁷Watson J. M. and P. and Weller R. Case of Bourneville's Tuberous Sclerosis. *Symmetrical Fibromatous Nodules of Face and Extremities* 10:644-6, 1939.

⁷⁸⁸Periz H. *Finnish Histopathology* 1: tuberous sclerosis. *Virchows Arch f. path.*

Anat. 278:690-702, 1930.

⁷⁹⁰Lufs H. Ueber den Zusammenhang der tuberösen Sklerose mit der Epiloia. *Virchows Arch f. path. Anat.* 278:690-702, 1930.

²⁰³⁰van der Hoeve J. Eye symptoms in Phacomatosis. *Tr. Ophth. Soc. U. Kingdom* 62:340-401, 1937.

The disease has frequently been encountered in families sometimes in three generations ^{2759 2792 793} and occasionally together with manifestations of Von Recklinghausen's disease ^{748 2792 2794 798} indicating the relationship of these two neurocutaneous syndromes which seem to be caused by unknown factors acting on the ectoderm



Fig 350 —Tuberous sclerosis (epiloia) Adenoma sebaceum in typical distribution along the nasolabial folds and on the chin (From Goodrich and Carls J Arch Dermat 1943)

Dermadromes —The best known dermatome of tuberous sclerosis is the *adenoma sebaceum* of the face. This dermatosis consists of more or less raised discrete hemispheric papules which are mainly arranged in the neighborhood

²⁷⁹¹Koenen J —Epilepsie familiäre, hereditäre Form von tuberöser Sklerose Acta psychiat 7 813 821 193

⁷⁹²Koenen J —Epilepsie familiäre hereditäre Form von tuberöser Sklerose Nederl tijdschr v geneesk 1931 I 731 738

²⁷Borreman Dyckmans and Van Bogaert —Forme héréditaire familiale de la sclérose tubéreuse J belge d neurol et de psychiatrie 713 746 1933 Zbl 48 406

⁷⁹⁴Wertheim-Moebius Pringle —Moebius-Recklinghausen und tuberöse Histioklierose Zbl 25 60 1931

²⁷⁹⁵Butteworth T and Wilson M Jr —Tuberous Sclerosis Dermatological Abstract Arch Dermat & Syph 43 1-41 1941

²⁷⁹⁶Bychowaki —Tuberöse Sklerose Wars aw Cz lek 8 4 9-463 1931 Zbl 186

²⁷⁹⁷Mukai J —Naevus sebaceus Acta dermat (Iyoto) 17 43-475 1931 Zbl 39 554

²⁷⁹⁸Fuhrs —Naevus Multiplex Pringle Zbl 45 15



of the nasolabial and mental folds. The symmetry is marked. The size of the individual lesions ranges from a few millimeters in diameter to almost a centimeter, the larger lesions being flatter and usually situated in the center of the group. The papules may vary in color and firmness. In the so called Balzer type the papules have the color of normal skin; in the Pringle type they are soft and red; and in the Hallopeau-Leredde-Darier type they are small and very firm.²⁷⁴⁹



Fig. 353.—Tuberous sclerosis: Large fibromatous nevus growth of the scalp. (From Good, O. H. and Garb, J. Arch. Dermat. 1943.)

The pathological differences are explained by the prevalence of the sebaceous glands, the vascular elements, or the fibrous stroma. Spontaneous regression has been observed in some cases but this is not the rule. The three types may be seen together.¹⁷⁴

Nevus slow growing pigmented plaques of a size which may cover for example the entire temporal area, and keratofibromatous leather-like plaques sometimes reaching palm size have been described.²⁷⁹⁻³⁰⁰⁻³⁰¹ The lumbar region is a favorite site for such nevus plaques and similar growths. The plaques show

²⁷⁴⁹ Dobkévitch, S. Adénomes. Nouvelle Pratique Dermatol. Vol. VI. Paris 1936. Masson & Cie.

²⁸⁰ Sachs, M. D. and Shaskan, D. A. Tuberous sclerosis. Am. J. Roentgenol. 53: 35-39, 1944.

²⁸¹ Turt, L. Tuberöse Sklerose. Hautveränderungen. Dermat. Wchnschr. 1934. I: 357-365.

pathologic changes similar to the adenomatous papules. They are not of the same diagnostic importance as the adenoma sebaceum.⁷³⁷⁻⁷⁶⁷

Slow growing multiple para ungual fibromas of small pea size especially of the toes⁸⁰³ have recently become known as a dermatome of tuberous sclerosis. The lesions which have a keratotic top bleed easily and may become troublesome. These tumors find their mucosal equivalent in lobulated fibromas of the gums.⁷⁶⁸⁻⁸⁰³ The nail substance may appear thickened or grooved lengthwise.⁸⁰⁴

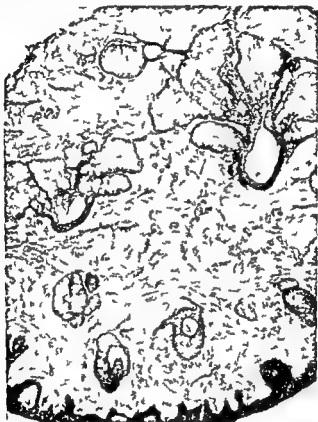


Fig. 344.—Adenoma sebaceum. (Courtesy Division of Dermatology, Department of Medicine, University of Chicago.)

Lipomas, syringocystadenomas, and some of the skin lesions known to occur in Von Recklinghausen's disease have also been found occasionally in tuberous sclerosis.

Frequently the adenoma sebaceum makes its appearance in the first decade of life,⁷³⁸ possibly stimulated by the same hormonal factor which causes the development of the sebaceous glands.

⁷³⁷Van Bouweldijk, Bastiaanse, F. S. Form familiale de sclérose tubéreuse. *J. belg. de Neurol. et de psychiat.* 23: 697-711, 1933. Zbl. 48: 404.

⁸⁰³Kurtz, L. Tuberosä Sklerose mit Hauterscheinung (subungual Fibrom an Fingern und Zehen, Rosacea des Gesichtes und lymphangiomatöse Fibrom an der Gingiva). *Zbl.* 43: 30.

⁸⁰⁴Loos, H. H. V. gel. Haut und Nails in kranken an Med. Klin. 26: 49-494, 1910.

Angiomatosis cerebri—Hemangiomas of the brain are frequently²⁷⁷
^{2805,2806} associated with vascular nevi of the face. While the nonactive nevus
 like hemangiomas are apt to be found in the cerebrum the growing angioblas-
 tomas usually develop in the cerebellum. Only the former seem to have related
 skin lesions while both develop eye manifestations though of different types.
 The nervous symptoms usually start very early sometimes during the first
 months of life.²⁸⁰⁷⁻²⁸⁰⁸ Contralateral jacksonian fits vertigo tremor disturbances
 of the gait and hemiplegia⁸⁰⁹ are the most obvious symptoms. Idiocy has also
 been observed.²⁸⁰⁷ The brain lesions may calcify and thus produce roentgeno-
 logic pictures²⁷⁷³⁸¹⁰ consisting of whorls and sinuous deposits in the gyri of the
 frontal and temporal lobes. Asymmetry of the face⁷⁷³⁻⁸⁰⁵ may accompany the
 unilateral brain changes.

The accompanying vascular nevi mainly occupy the face. They seem to
 be more often unilateral than bilateral. They are large even enormous²⁸¹¹ single

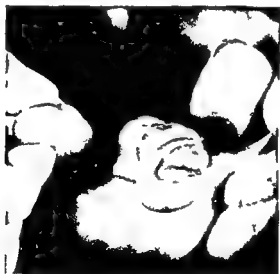


Fig 355A.—Fibroma of the nose in tuberous sclerosis and adenoma sebaceum. (Courtesy Division of Dermatology Department of Medicine University of Chicago.)

²⁸⁰⁶Krabbe K H Facial and Meningeal Angiomatosis With Calcifications of the Main Cortex
Arch Neurol & Psychiat 32 737 '5 1934

²⁸⁰⁵Ufer H Ueber hereditäre Angiomatose des Gehirns und der Rinde ihre Beziehungen
 zu einander und zur Angiomatose der Haut *Ztschr f ges Neurol u Psychiat* 113 651-686 1934

²⁸⁰⁷Meyer F Gesichtshämangiom und Gehirnrindenangiom *Monatschr f Psychiat u
 Neurol* 92 94 208 1936

²⁸⁰⁸Schaefer W Ueber einen Fall von halbseitigem Ethmoidal- und Hämangiom *Monatschr f
 Kinderh* 50 35-44 1931

²⁸⁰⁹Kreyenberg H and Hantsch I Hämangiom mit Rindenangiom des Gehirns und Hydro-
phthalmu *Z Neurol* 152 761-7 1935

²⁸¹⁰Schwartz C W Vascular Tumors and Anomalies of the Skull and Brain From a Roentgeno-
 logical Viewpoint *Am J Roentgenol* 41 881-900 1939

²⁸¹¹Ironsides R and Hill D Cutaneous Naevus With Buphthalmos and Epilepsy *J Ment Sc*
 87 631-634 1941

or multiple telangiectasias of port wine stain or tumor type sometimes involving the oral mucosa and even the pharynx²⁸¹²

The nevi are often, but not necessarily on the side of the hemangioma of the brain^{2813, 2814}

Besides the telangiectatic lesions nevus anemicus has been recorded in several instances²⁸¹⁴ Pigmented nevus of one side of the face and ipsilateral glioma has been seen by Meirowsky²⁸¹⁵



Fig 35 ■ —Tuberous sclerosis / Fibromas of the nailbeds with grooving of the nail. (From Noon Z ■ Arch Dermat 1934)

Heredity is an etiological factor²⁸¹⁶ Occasional combinations with the other neurocutaneous diseases have been reported^{2817 2818 2819}

The term Parke's syndrome is sometimes used for the combination of cerebral and cutaneous hemangiomas with epilepsy and idiotism

²⁸¹²Tyson H H Nevus Flammeus of the Face and Glioma Associated With Glaucoma Vascular Changes in the Ili and a Calcified Vascular Growth in the Left Occipital Lobe With Homonymous Hemianopia Arch Ophth 8 365-371 1932

²⁸¹³Ellis H W B T Igeminal Na vu and Hemangioma of Meninges Proc Roy Soc Med 25 1732 1734 1932

²⁸¹⁴Weber F P and Harris K E A Case of Widely Distributed Superficial Telangiectatic Naevus Associated With Area of Na vu Anaemia Indication That a Portion of the Cerebral Meninges are Similarly Involved Brit J Dermat 61 77 83 1957

²⁸¹⁵Meirowsky E Halbehtige Na vu bei einem Epileptiker (Klinische Licht) Zbl 40 24

²⁸¹⁶Touraine A and Guyot Van Yang État dysraphique familial Bull Soc Franç d dermat et syph 11 1550-1561 1936

²⁸¹⁷Oreig H M Case of Meningeal Na vu Associated With Adenoma Sebaceum Edinburgh M J 28 105-111 1927

CHAPTER XXXIX

DISORDERS OF THE NERVOUS SYSTEM

Diseases of the Spinal Cord

Cord lesions may regardless of their nature produce *pigmentations*. Such melanoses in the area of the skin supplied by the injured parts of the cord have been observed after gunshot injuries during the first world war. Andre Thomas¹¹ found an increase of the pilomotor and sudomotor reflexes in the pigmented areas which suggests that the sympathetic system plays a part in the etiology of the pigmentations. The pigmentations may appear after two weeks (Simons after E. Kaufmann¹²) or after months or even years. Szczy¹³ feels that the slow appearance of the lesions makes a sympathetic etiology unlikely. Since most of the cord injuries are fatal before the pigmentation has a chance to develop observations have remained rare. Depigmentations of the skin after injuries or other lesions of the spinal cord e.g. tumors have occasionally been seen^{11, 12, 13, 14}. In one case there was red dermographism above and white dermographism below the level of the injury.

E. Guttmann¹⁵ points out that the fibers conducting the sensations of touch and position ascend directly without crossing while the pathways for the perception of warmth and pain enter a second neuron and cross to the other side. This explains the fact that a unilateral lesion of the spinal cord causes a contralateral anesthesia for warmth and pain. Localized destruction of the gray matter of the cord also causes abolition of the perception of warmth and pain with preservation of the senses of touch and position. This dissociation can be seen in several localized cord lesions e.g. in syringomyelia hemorrhage into the gray matter and in intramedullary tumors. The sensibility above and below the level of a circumscribed intramedullary lesion may be undisturbed if no direct fibers are involved. Complete transverse lesions of the spinal cord leads to anesthesia below the level of the corresponding cutaneous innervation. The lowest segments however often retain some sensibility.

Status Dysraphicus—Status dysraphicus^{16, 17} is a hereditary condition characterized by a great number of malformations. The name is derived from the pathogenesis of the leading anomaly, spina bifida caused by failure of the embryonal closing of the raphe of the medullary groove. Funnel chest disproportion between trunk and extremities abnormally long arms clubbed hands

¹¹ André Thomas. La pigmentation de la peau dans les blessures et les affections de la moelle. Rev. neurol. 28 102 10 19 1.

¹² Brenner F. W. Untersuchungen zur Aetiologie der Syringomyelie. Status dysraphicus. Deutsche Zeitschr. f. Nervenhe., 88 1 19 6.

¹³ Breime F. W. Pathol. anatom. Begründung des Status dysraphicus. Deutsche Zeitschr. f. Nervenhe. 89 104 1927.

and clubbed feet polyastia asymmetry of the breasts and web formation are some of the stigmata Debility epilepsy psychoses acrocyanosis cataract hypogenitalism Horner's syndrome heterochromia of the iris and other disturbances may accumulate in one individual but more often such symptoms are grouped in families.

Spina bifida occulta occurs in about 17 per cent of all persons a fact which has become known only with the advent of the x ray.¹¹ Lumbar nevi and circumscribed sometimes excessive hypertrichosis over the spine may indicate the underlying cleft formation.



Fig 356 Topographic relationship of spinal cord to vertebral column and on radiograph.

Familial Trophiedema—There also exists a relationship between status dysraphicus and the chronic familial trophiedema of Nonne Milroy and Meige.^{11, 12} This is a hereditary condition which has been observed in as many as five generations,¹³ though never in many members. The disorder affects

¹⁰⁰ (Artikel) und Lorenz: Klinisch-physiologische und bakteriologische Untersuchung an 35 Fällen von Stomatodysraphie und 11 Fällen von Stomatodysraphie. Ztsch. f. d. ges. Med. 1923.

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the female sex more frequently than the male^{23 25 27 28} The trouble is some times congenital but more often it starts later in life frequently in adolescence rarely later A slowly progressive later stationary edema develops in one or both legs rarely in the arms Painful febrile attacks have been observed to increase the edema^{25 28} The fully developed lesion consists of an enormous firm edema The skin is smooth white or bluish or with a vascular pattern and feels cool Folds cannot be raised The contour of the legs is usually com



Fig. 3.7 — Patch of hair over spina bifida

pletely lost A deep fold separates the leg from the foot The condition does not endanger life as shown by Meigs's second report on the same case 35 years after his first presentation At the time of the second report the afflicted woman was 75 years old without other trouble than the edema

²²⁷Moniz E Sur l'etopie d'eme chronique de Meigs—Nouveaux cas—Considerations sur leur etiology Rev n urol 28 1046 109 10 1

²²⁸Tauber E Milroy's Disease Arch Dermat & Syph 23 1127 1128 1931

²²⁹McGuire J and Zeek P Pathogenesis of Chronic Hereditary Edema of Extremities (Milroy's Disease) J A M A 98 870 873 1932

Besides status dysraphicus hypothyroidism^{25 2851} hyperthyroidism^{25 832} hypogonitalism,^{24- 833} and melorheostosis Léri²⁴ have been found in association with the edema but no definite etiology has been established. The dominant pathological feature is loss of the subepidermal elastica increase of collagenous fibers and widening of the lymphatic spaces. No effective therapy is known.



Fig. 359.—Spina bifida. X-ray of part of with patch of hair over lumbar spine.

Syringomyelia is much more closely related to status dysraphicus. Curtius and Lorenz²⁶ found among 17 cases of syringomyelia 11 instances of spina bifida occulta. In the families of patients afflicted with syringomyelia anomalies of the breasts and mental disorders are relatively common.

Increase of neuroglia (gliosis) in the spinal cord and formation of tube-like cavities within these lesions lead to a great variety of neurological symptoms.

²⁴⁵¹ Vimeash, M. A. Trophœdema (M. Ig.) Zbl. 27: 546, 1904.

²⁴⁵² Průšek, F. Melorheostose. Krankh. u. Česká dermat. 12: 255-99, 1931. Zbl. 40: 526.

²⁴⁵³ G. Blüsch, F. Über eine Kombination von Trophœdema (M. Ig.) mit Melorheostose. Léri. Dermat. Wchnsch. 88: 1761-1766, 1909.

²⁴⁵⁴ Slavin, M. A. Ein Fall von Trophœdema. Über die Beziehungen zur Menstruation. Zbl. f. Gynäk. 81: 229, 1907.

varying with the sites within the central nervous system. There occur sensory disturbances, muscular atrophy beginning in the intermetacarpal muscles of the hands and ending up in characteristic contractions, skeletal damage, eye symptoms, and spasms. The course of the disease is very slow; the first symptoms usually remaining unrecognized over several years. The patients rarely die of syringomyelia but they often succumb to intercurrent infections.¹³³⁴ Recovery hardly ever occurs.



Fig. 3 —Nonne Melke Milroy disease. Female aged 43 years. Only mild pituitary symptom—swelling of leg from childhood, became worse at puberty. Mother had the same trouble. (Courtesy Wilcoxon in General Hospital.)

Dermadromes—The dermadromes of syringomyelia are mainly due to the fundamental disturbance, dissociated anesthesia. While the perception of pain and temperature become lost, the sense of touch and deep sensibility remain undisturbed. Paresthesias are common in the early stages and the attempt to treat them with heat has often caused the first painless burns. Circulatory and possibly trophic influences may also play a part.

¹³³⁴Ding R. and Haymaker W.: Nervous Diseases. St. Louis, 1939. The C. V. Mosby Co.

The patients hardly ever escape the traumatic and infectious complications. In advanced cases the hands are rarely found free of crusty sometimes rhagadi form ulcerations of varying sizes often located on the extensor surfaces of the fingers. Such trophic ulcers may lead to painless destructive lesions around the nails. Mutilation resembling leprosy may ensue. These fairly characteristic finger affections are called *pinaris analgésiques*. Transitory edema of the Quincke type^{3520 66 3663} as well as lasting swellings represent another feature. These swellings are often found on the hands giving them a succulent appearance. The edema may disappear and leave a flaccid atrophic skin with a silky or papyraceous surface or it may lead to a leathery uneven hypertrophy and hyperkeratosis unrelated to pressure or work (lizard skin). The appearance of unusual keratoses on the hands should make the physician think of syringomyelia. Regional³⁷⁵ eruptions of large bullae in moderate numbers and unrelated to trauma may cause necrotic ulcerations^{376 377} another parallel to leprosy.

The nails may become affected in many ways. Hypertrophy and atrophy anomalies of position white color brittleness groove formation and complete loss have often been described^{353 322}. The hair may gray early.

The treatment is symptomatic. Protection from trauma especially burns is most important.

No skin manifestations were observed in 81 cases of amyotrophic lateral sclerosis³⁸³⁹ though symmetric pigmentations of the forearms had been described earlier (Bowing after E. Kaufmann^{11 5}).

Diseases of the Brain

A variety of dermatomes may be seen as results of cerebral lesions.

Apoplexy may be followed by unilateral sweating of the paralyzed side (Binger and Berg after Marchionini^{66 663}). This has been called *hémiplegie sudorale*. The galvanic skin reflex (Veraguth Tarchanoff's phenomenon) can not be elicited on the paralyzed side²⁵⁴⁰.

Localized or unilateral swelling dryness and in about half of the cases scaliness occur. Unilateral jaundice³⁴¹ occurs in *apoplexy* (See Chapter on Liver).

³⁵²⁰Schirne H. Hyperkeratose und Rhagadiellen. I. Überwachungsbeobachtung bei Syringomyelie. Arch. f. Dermat. u. Syph. 173: 27-33, 1935.

³⁵²¹Spillmann L. Lésion du malade atteint de ga. grès cutané. Origine syringomyelique. Rev. méd. de l'est 49: 260-19, 1912, 50.

³⁵²²Blaszyk R. Syringomyelia Associated With Trophic Destructive Bulla. Arch. Dermat. & Syph. 111: 1094-1095, 1936.

³⁵²³Frühwald. Syringomyelie. Zbl. 45: 97.

³⁵²⁴Wechsler J. S. et al. et al. M. R. and Stein A. Primary and Symptomatic Amyotrophic Lateral Sclerosis (151 Cases). Am. J. M. S. 208: 70-91, 1944.

³⁵²⁵Essen H. W. and Iodonta H. H. Ablauf d. galvanisch n. Hautred. es bei halbseitig n. Hirnleiden. Deutsch. Ztschr. N. 128: 34-4, 193.

³⁵²⁶Jag. I. H. Ipsilateral Fd m. and Contralateral J undiv. Associat. i With H. miplegia and Cardi. n. Decomensation. Am. J. M. S. 177: 3-76, 1929.

Brain injuries may cause contralateral coating of the tongue^{83 84} also *pecia*¹⁰⁷ and sudden unilateral graying of the hair and beard (Gowers after J A M A²⁸⁴⁴)

Wartenberg²⁸⁴⁵ observed isolated pruritus of the nose in *tumors* of the temporal lobe. He considered the itching and compulsory scratching of the nose which persisted in deep sleep as a valuable temporal lobe symptom but other neurologists²⁸⁴⁶ deny its localizing value.

Other occasional observations are unilateral seborrhea and sweating *ecchymoses* vitiligo and other pigmentary disorders of the skin^{286 863} (See also neurocutaneous diseases.)



Fig 360 - Unilateral edema of the face on paralyzed side. Three year after hemiplegia.

*Urticaria factitia*²⁸⁴⁸ is supposedly pronounced in idiopathic *epilepsy* but not in the jacksonian type. During the epileptic fit the galvanic skin resistance is reduced²⁸⁴⁷.

The epileptic seizure may be preceded by vasomotor symptoms like blushing or pallor. The acute spasms of the respiratory muscles and the concomitant increased pressure in the vena cava may cause petechiae.

These are often found in the conjunctivae and in the skin of the neck, the chest and behind the ears²⁸⁴⁹. The petechiae are rarely numerous (ecchymotic mask)⁸⁴⁸ but they have some diagnostic or forensic value²⁴⁹. Chloasma in the shape of the forehead ring occurs occasionally in epilepsy. (See Encephalitis.)

Börnstein W. Trophisch Veränderungen in der Zungenschleimhaut (herdgetrennt r Zung n belag) bei cortikalem Herd. Z. Neur. 104: 776-799, 1926.

⁸⁴ Levinger E. Unvollständiger Zungenbelag als vasomotorische trophische Störung. Deutsche med. Wochenschr. 52: 1: 707-708, 1926.

⁸⁴ Vitamins and Human Gray Hair. Editorial J. A. M. A. 122: 875-876, 1943.

²⁸⁴⁵ Wartenberg R. Ein Schließlappensymptom. Arch. f. Psychiat. 103: 321, 1935.

⁸⁴ Camarér A. F. Diagnostisch Wichtigkeit der ödematösen oder urticariformen Dermographismus in der Neurologie. Acta Conf. lat. Amer. Neur. etc. 1: 93-110, 1929. / bl. 38, 189.

⁷ Porter J. M. Jr. Galvanic Skin Phenomena in Epileptics. J. Gen. Psychol. 11: 24-44, 1934.

²⁸⁴⁸ De Blasí A. Sulla cosiddetta maschera ecchimotica. Ann. Ital. di chir. 13: 493-510, 1934.

²⁸⁴ Millan F. Piqueté purpurique au couvicothèque des crises comitiales. Rev. franc. de dermat. et de vénér. 4: 137-138, 1928.

Traumatization of the central nervous system may cause *purpura* of a distribution which is apparently governed by the nervous system. *Purpura* up to the level of a spinal anesthesia⁸⁰ or generalized symmetric *purpura* after skull fracture⁸¹ pertain here.

Purpuric lesions have been described in many organic diseases of the central nervous system especially in multiple sclerosis²⁸.

Diffuse *hypertrichosis* has been observed in encephalitis following complicated fractures^{28,3} in glioma of the temporal lobe³⁴ in disseminated sclerosis^{28,5} and in several other lesions of the brain. Hirsutism of this type may disappear with recovery.

Encephalitis lethargica (Von Economo's disease) is an epidemic and contagious disease probably caused by a filterable virus. After an incubation period of approximately a week the disease breaks out with mild fever and influenza resembling symptoms, often with icterus.

Meningitic symptoms are lacking or mild but ocular palsies and headache develop frequently.

In the course of a week sleepiness or irritability increases. In the lethargic type the patient sleeps most of the daytime. He can be aroused only with difficulty. At night he is often restless. In the irritable or hyperkinetic form the muscle tone is increased. Tremor spastic paralysis fever and delirium are the main symptoms. The acute stage may last several weeks or months. The mortality of the cases with a stormy onset may be as high as 33 per cent.

Another third of both types may recover completely and one third develops progressive or stationary sequelae among which Parkinsonism with paralysis agitans like symptoms rigidity salivation tremor is the most common one (Von Economo after Bing and Haymaker³³).

In young individuals change of character hypomania and psychoses may follow. The pathological characteristics are inflammatory infiltrations and hemorrhages in the gray matter of the large nuclei and the frontal lobes.

Dermadromes—Best known among a variety of skin manifestations of encephalitis lethargica is the profuse *seborrhea*^{28,6} which has been found in from 35³⁷ to 48 per cent (Stern after E. Guttmann³⁸) of the cases. Rattner³³ found unusual oiliness of the face in only 8 per cent. This symptom has rarely been seen in true paralysis agitans.

⁸⁰ Post F. Purpura nach Lumbarlithese. Klin. Wochenschr. 1931. II. 2341-2342.

⁸¹ Koller W. Zur Frage der Purpura traumatica. München med. Wochenschr. 75. 5. 15. 4. 19. 8.

²⁸ Schindler R. Nerven system und Spontane Blutung. Berlin. 19. 7. 8. Jäger.

³³ Cacciatore B. Gliomi del cervello con tropismo catatonico. Atti del 1° Congresso Internazionale di Neurologia. 1931. 113-116.

³⁴ Markoff N. Hirsutism in Woman. With Glioma of Left Lobe of Brain. Schweiz. med. Wochenschr. 69. 55-57. 1939.

³⁵ Leong F. The Fatwickles of Hypertrichosis. Brit. J. Derm. 60. 19. 0.

³⁶ Cohn T. Facial Hirsutism. Lethargic with endocrine Cripples. J. Clin. Neurol. 60. 19. 0.

³⁷ W. H. H. Seborrheic Dermatitis. Post. Epileptic Encephalitis. Arch. Dermat. & Syph. 60. 1930.

³⁸ Rattner H. Changes in the Skin in Chronic Encephalitis. Arch. Dermat. & Syph. 31. 35-37. 1935.

In typical cases the face appears as if it were covered with grease. If the grease is wiped off it reappears within about 20 minutes. Facial puffiness³⁴⁶ and complicating seborrheic dermatitis is not uncommon.³⁴⁷ Seborrhea is comparable to other disorders of secretion like hyperhidrosis and excessive salivation and lacrimation which may cause chronic blepharitis and dermatitis of the lids. The cause of the seborrhea is supposedly an inflammatory irritation of a center in the wall of the third ventricle.³⁴⁸ Perutz³⁴⁹ could produce seborrhea in rabbits by stimulation of the interbrain.

*Trophic ulcers*³⁵⁰ mostly in the nasolabial folds or around the nasal orifices sometimes invading the nasal septum and the upper lip have often been described.³⁵¹ The lesions may be very destructive and hard to cure.



Fig 361



Fig 36

Figs 361-36 —Bow forth adri g n i cephalitis lethargica (Courtesy of Dr H. Haxthausen, Copenhagen)

These postencephalitic ulcers have in some instances been mistaken for rodent ulcers. The sensitivity of prur and touch is preserved.³⁵² Analogous ulcerations in other areas e.g. the hands³⁵³ and the tongue (Schirmer and

³⁴⁶Stieffer G. (a) Seborrhoea facialis ein Symptom der Encephalitis lethargica. Z. Neur. 73 455 1911. (b) Seborrhoea facialis isolierte postencephalitishe Veränderung. W. in klin. Wchenschr. 334 1914.

³⁴⁷Perutz A., Lustig B. and Klein A. E. Zur zeitl. u. Regulierung d. Fettstoffwechsels der Hautoberfläche. Arch. f. Dermat. u. Syph. 170 511 5 0 1931.

³⁴⁸Hoffman H. Large Trophic Ulceration of Nose and Mouth Following Lethargic Encephalitis (Parkinsonism). Deutsche med. Wchnsch. 52 238 239 1926.

³⁴⁹Rosenberg S. J. and Solovay J. Trophic Ulcer Following Encephalitis Lethargica. Arch. Dermat. & Syph. 39 9 5 9 1939.

³⁵⁰Michon P. Trobles trophiques cutanés et buccaux sensitifs locaux. Bull. Soc. franç. de dermat. et syph. 38 1083 1094 1931.

Baumann after Marchionini^{66 663}) are much rarer. The localization in the nasolabial folds suggests a connection with the seborrhea which is most active in this site.

*Chloasma*⁶⁴ especially in the form of the brown forehead ring has been found repeatedly^{65 8}. Such chloasmatic pigmentations are also known to occur in other intracranial processes = g. epilepsy. The typical brown forehead ring has the shape of a crossbow, closely paralleling the hairline in the center and descending symmetrically toward both lateral ends of the eyebrows. A nonpigmented zone separates the hair as well as the eyebrows from the lesions.

Other reports on postencephalitic dermatoses include symmetrical gangrene^{66 663 666}, urticaria facticia, Quincke's edema²⁹⁶⁶, multiple paronychias (Schirmer after Marchionini^{66 663}), severe subungual hemorrhages²⁹⁶⁷, diffuse alopecia resulting in almost total baldness in 4 cases²⁹⁶⁸, bullous eruptions²⁹⁶⁹ and Herpes Zoster⁶⁸ in 16 cases.

⁶⁶⁴Haxthausen H. Skin Changes Following Encephalitis Lethargica. Acta dermat. venereol. 13: 409-416 1937.

⁶⁶⁵Anderon O. and Wernoe T. B. Der braune Stirnring. Legak. f. Laeger 1930 II: 817 & 1. Zbl. 36: 214.

⁶⁶⁶Düchler P. Vasomotorische ophthalmische Störungen bei Encephalitis epidemica. Gyogyaszat 51: 718 1933. Zbl. 12: 174.

⁶⁶⁷von Poo J. Hamatom der Nasenbest. bei postencephalitischem Parkinsonismus. Dermat. Wechschr. 1931 I: 45.

⁶⁶⁸Stiller G. Zur Klinik der Encephalitis lethargica. Wien klin. Wchnschr. 1931 36: 259 1930.

⁶⁶⁹Netter A. 16 observations de zones dans l'encéphale léthargique. Zbl. 36: 13.

hirsutism²³⁷⁶ The latter observation is in contrast to Kretschmer. However there is a general impression that some degree of hirsutism is found relatively often in various psychoses.⁸⁷⁷⁻⁸⁷⁹

E *Alopecia totalis* may occur in connection with depression⁸⁸⁰ however the depression may also be of a reactive character due to the disfiguring loss of hair.

Heller⁵⁵⁸ was unable to confirm earlier claims of unexplainable and characteristic nail changes in psychoses. It is an old belief that the insane have long or unusual nails, but this is not true*. The transverse lines can usually



Fig 363 - Mental tardation. Fur cap hair line. (Courtesy Wisconsin General Hospital)

be traced to intercurrent disorders. Under proper care the nails of the inmates of asylums may be in better condition than the nails of the average population.

Repeated loss of the nails and of the hair in circular psychosis has been described (Trusfontaines after Heller⁵⁵⁸).

The same hood was the thing fulfilled upon Nebuchadnezzar, and he was driven from men, and did eat grass as oxen, and his body was wet with the dew of heaven till his hairs were grown like eagle feathers, and his nails like birds' claws. - Daniel IV, 33.

⁸⁷⁷Mumford I. H. and Chvostek L. C. F. An Investigation into the Physical Characteristics of the Clinician's Types of the Body. J. Ment. Sci. 78: 34-35, 1931.

⁸⁷⁸Elliott H. F. Comparison of Non-psychotic Women With Schizophrenics With Respect to Body Type. Sign. of Autonom. Imbalance and Mental History. J. Psychiat. Qu. 15: 1-2, 1911.

⁸⁷⁹Epstein A. L. Somatological studies in Psychiatry. J. Nerv. Ment. Dis. 143: 56-59, 1933.

⁸⁸⁰Jarcho C. J. Ballif C. and Caveman Z. F. The autonomic system in the case of a violent epileptic. Rev. franç. d'encéphal. 2: 17-18, 1953.

⁸⁸¹Allen C. and Carlyle-Gall L. Depression Hypothetical Alopecia Syndrome. Brit. M. J. 2: 194, 1947.

The observations on the status of the skin in the insane have not yielded many tangible results. Vascular symptoms are first on the list. Kretschmer²⁷⁰ also Mumford and Chevens²⁷¹ emphasize the rosy complexion of the circular pyknic in comparison with the pale asthenic schizophrenes.

The vasomotor lability of the pyknic also expresses itself in a greater tendency to blushing and rosacea. Some authors found the skin of the circular in good condition rather moist with a well developed prunniculus adiposus. The skin of the schizophrenic is usually *paler, flaccid and unhealthy*. Acne is frequent.²⁷² Dryness and a *keratotic* tendency has often been considered a characteristic of the skin of the insane.²⁷³ Mumford and Chevens²⁷⁴ relate this symptom to the schizophrenic.



Fig 364—Mental disability. Female aged 4 years. Hypertrophic.

The most important vascular phenomenon of the schizophrenic is *acrocyanosis*. This has been confirmed by many writers.²⁷⁵⁻²⁷⁷ Closely related to the acrocyanotic syndrome is the pseudo edema of the insane (Dide Trepsat Krepelin after Simon²⁸³). In acrocyanosis the *acra* are bluish with red vascular patterns cold slightly swollen but not pitting. The swelling may reach up to the knees and a fold may be marked at the ankles and at the base of the toes. There is prolonged white dermographism with red borders lasting from one and a half to two hours.

Red dermographism is common in a great variety of psychoses.²⁸⁴

Generalized addisonoid *melanoderma* in catatonic schizophrenia has been observed in several instances.²⁸⁵

Spontaneous and unexplained bullae with subsequent ulcerations occur even in bedridden patients without undue exposure to traumatism. In the *mentally deficient* anomalies of the hair pigmentation acrocyanosis pseudo

²⁷⁰ Goldblatt H and Bermann S. *Quelques observations de la peau chez les aliénés*. Schweiz Arch. Neurol. & Psychiat. 11: 234 11 19 6.

²⁷¹ Stern E. *Etiology and Pathology of Acrocyanosis*. Brit. J. Dermat. & Syph. 49: 100 108 1937.

²⁷² Simon C. *Dermatoses en rapport avec des troubles du système nerveux*. Nouvelle pratique dermatologique vol. 5. Paris 1936. Masson & Cie pp. 749 767.

²⁷³ Petrocelli M. *Il dermographismo nelle psicosi*. Chir. Vello 11: 40-46 1932. Zbl. 42: 83.

²⁷⁴ Wigert V. *Il catatonie un il Melanodermie*. Acta psychiat. (Stockh.) 1: 84 144 1926. Zbl.

edema malformations, new hemihypertrophy²⁸⁶ and scars from biting the hands and wrists⁸³⁷ have frequently been recorded but the statistics are controversial and⁵⁷⁶ some lack sufficient controls. Mumford and Chevens⁸ emphasize the juvenile character of the skin in mentally retarded adults.

The dryness of the skin and hair the tendency to eczematous eruptions the large protruding tongue malformations of the ears epicanthus and mongol spots⁸⁸⁹ are the well known external signs of *mongoloid idiotism*. Familial vero derma pigmentosum may be associated with severe retardation.⁸⁹⁰

Psychogenic Dermatoses

A great number of *cutaneous reactions to psychic stimuli* are known. One has to assume that the autonomic system mediates the psychic impulses to the effector organs in the skin by the liberation of acetylcholin or sympathin (See autonomic system). Pallor blushing perspiration gooseflesh and the gray- ing of the hair are proverbial phenomena caused by fear shame rage embarrassment excitement worry and other psychic factors. Certain sensa- tions in the skin like spine tingling shuddering itching and hair raising may also be produced by merely psychic causes e.g. reading an exciting story fear acoustic stimuli as sour notes and shrill sounds or the touching of certain ma- terials like silk cardboard and rough wood. Using laboratory methods very sensitive responses can be demonstrated. Not only actual sensations but even the mere imagination of a sensation like pain reduces the electric resistance of the skin in a typical way which is demonstrable by Tarchanoff's psycho-galvanic reflex. This accurately measurable drop in electrical resistance is due to the sympathetic stimulation of the sweat glands.⁶¹¹

The skin temperature depends on the arterial tonus which responds readily to psychic stimuli. A local temperature increase of 0.2 centigrade can be caused by mental concentration on a spot.²⁸⁹¹ The famous lie-detector is based on such psychogenic reactions in the skin and other organs. It is not difficult to conceive that inflammatory processes which are so intimately related to vasodilation may in some instances be produced by psychic causes. Many experiments have proved the truth of this assumption. There are many clinical observations which support the *psychogenic etiology of some dermatoses* but it is more often true that psychic stimuli enhance or impair an existing dermatosis than that they actually cause it. The experimental methods do not try to explain the psychic part of the sequence, emotion—somatic changes. They concentrate on the latter part. The greatest attempt, not to explain or to locate the psychic

NEWARK, N. J. - G. C. G. Ital. Hypertrophy of Left Ventricle. Circ. 4 m. a. 1. Hand With Nervous System. Am. J. N. 4. 171. 560-5. 5. 19. 6.

⁴ Butterworth Th. ni Wilson M. Jr. Incidence of Diseases of the Skin in Freely Minded
F. Res. Arch Dermat & Syph 28: 203-209 1939

Stigmata of Degeneration in Relation to Mental Disease. — Proc Roy Soc Med 31: 413-48, 1938

*De Sa tis I d Caechlon A I Ill zia erod rma. Riv sper di I nlat 66 269-772

27 209-2 1 10¹⁰ Pay hisch Beel flumung 1 r Hautt mperatu Journ f Psychol u Neurol.

but to permit a glimpse of its mechanisms has been made by Freud and his psychoanalytic school

According to this doctrine the powerful source of psychic energy the mystic Id makes contact with somatic processes somewhere in the form of instincts. A resistance is set up against the demands of the instincts (Freud after Hinsie and Shatzky²⁸⁹). This leads to conflicts because the suppressed or repressed instincts are not deprived of their power. They continue to seek discharge comparable to potential energy which tends to transform itself into kinetic energy. Somatic processes including disease may be one of the forms of transformation. In this way conflicts may lead to disease. The term psychodermatosis* seems appropriate for dermatoses of psychogenic origin.

The case material illustrating the psychogenesis of dermatoses is large but not always conclusive. Small numbers, the fluctuating course of the dermatosis in question, and accompanying dermatological treatment often obscure the evidence which is supposed to prove psychogenesis. But in spite of these limitations the existence of psychogenous dermatoses and the value of psychotherapy cannot be denied.^{291 292 293}

Vascular Phenomena—Psychogenic *erythema* as an expression of modesty, embarrassment or excitement is usually restricted to the face and neck. About the neck or upper chest it may assume a blotchy pattern especially in women who generally are much more likely to blush than men. Children of both sexes seem to blush equally with various emotions especially with guilt on telling a lie. Emotional erythema has been seen in atypical sites to which the mind of the patient had been concentrated. A patient blushed emotionally around a tuberculous sinus of long standing.²⁸⁹ A woman who is examined gynecologically for the first time may show emotional erythema on her abdomen.^{289 292 293}

The word neurodermatosis should be restricted to the dermatoses of organic disease of the nervous system. The word neuro is often being used for a relatively minor disorder of the psychic constitution which is not a psychosis.

²⁸⁹ Hinsie L E and Shatzky J J. Psychiatric Dictionary New York 1940 Oxford University Press.

²⁹⁰ Guck W T. Psych und Haut Handb d M u Lk 4 130 149 1933.

²⁹¹ Gillespie R B. Psychological Aspects of Skin Diseases Brit J Dermat 56 116 1933.

²⁹² Mayr J J. Ubc Psychogenes von Hautkrankheiten Zbl 23 1 19.

²⁹³ Klause J V. Psychogenic Aspects of Diseases of the Skin Arch Dermat & Syph 30 851 853 1934.

²⁹⁴ MacKee G M. Neurotic Eruptions Arch Dermat & Syph 1 256 19 0.

²⁹⁵ We the J. Di neurotischen und hysterischen Dermatosen Dermat Wchnschr 1933 I 461-470 513 518.

²⁹⁶ Pusey W A and Senar F E. Eruptions Cases Arch Dermat & Syph 1 19 0 19 0.

²⁹⁷ Michelon H E. The Motivation of Self Induced Eruptions Arch Dermat & Syph 51 245-2 0 1915.

²⁹⁸ Obermayer M E. Functional Factors in Common Dermatoses J A M A 122 86 1943.

²⁹⁹ Lynch H W Hinckley H G and Gowan D W. Psychobiologic Studies of Patients With Atopic Eczema Arch Dermat & Syph 51 51 60 1945.

³⁰⁰ van der Erve J M and Becker S W. Functional Studies in Patients With Neurodermatoses J A M A 105 1098 1935.

Blushing and fear of embarrassing blushing can sometimes be traced to early sexual emotions. The psychoanalysts found an underlying Oedipus complex in some pronounced cases.⁸⁹⁴

Psychogenic hemorrhages may be caused by a gruesome sight⁸⁹⁵ or similar experiences. Schindler⁸ who has devoted a monograph to the subject of spontaneous neurogenic and psychogenic hemorrhages saw the purpuric spots most often on the lower legs of hysterical persons.

He describes three cases which were cured by hypnosis or psychotherapy. The purpuric lesions could be provoked by hypnotic suggestion.⁸⁹⁶ Kohnstamm could inhibit bleeding from needle pricks by the hypnotic suggestion that the pricked left index finger would not bleed. The pricked index finger of the right hand for which normal conditions had been suggested bled in the usual manner.⁸⁹⁸

Mystic Stigmatization—In this connection the phenomenon of *stigmatization* has to be mentioned. The term is derived from the sixth chapter of the Epistle to the Galatians in which the Apostle Paulus says: I wear the mark (stigmata) of the wounds of Jesus on my body.^{899 900 907} Thus it means the appearance of skin lesions resembling the wounds suffered by Jesus during the crucifixion.

The numbers of more or less well acknowledged cases vary from 80 to 321 according to various Catholic sources.⁹⁰³ The Catholic church has at least in modern times exercised great skepticism in this matter. The most famous and if Saint Paul's word is not taken literally probably the first of the stigmatized was Saint Francis. Sixty-two have been beatified or canonized. A medical report of an eighteenth century case of stigmatization including autopsy has recently been made accessible.⁹⁰² Twenty-nine cases occurred in the nineteenth century and at least three have been observed by trained modern scientists. The last case was that of the still living Theresa Neumann of Konnersreuth in the Bavarian Palatinate. The case probably resembled earlier observations in many respects.^{906 907} Ewald⁹⁰⁸ professor of psychiatry at the University of Erlangen who observed Theresa and furnished a now famous expert opinion for the physician of the bishop of Regensburg saw nickel-sized dry scab-covered hemorrhagic and tender lesions on the dorsa of the hands and feet. The scabs developed from blood which oozed through the thin epidermal membrane during the ecstasies. There were smaller lesions on the corresponding spots of the palms and soles and over the heart next to the sternum. The latter the so-called chest wound had a slightly raised edematous appearance.

⁸⁹⁴Werth J. A Symposium on Psychogenic Dermatoses. Dermat. Wchnschr. 94: 70, 1932.

⁸⁹⁵Jakobi W. Die Stigmatisierten. Beiträge zur Psychologie der Mystik. Grazfragen d. Nerv. u. Geisteslebens. No. 114 pp. 1-57. München. III. 3. J. P. Bergmann.

⁸⁹⁶Schult J. H. Stigmatization. Deutsche med. Wchnschr. 82: 1541-1556, 1907.

⁸⁹⁷Simon C. Les stigmates cutanés des mystiques. Bull. méd. Paris 47: 667-671, 1913.

⁸⁹⁸Ewald G. Die Stigmatisierte von Konnersreuth. Untersuchungsbericht und gutachtliche Stellungnahme. München. med. Wchnschr. 74: 1951-1997, 1927.

The American dermatologist Klauder,²⁹⁹ who examined Theresa nine years after Ewald²⁹⁸ found a remarkably square dry glazed hemorrhagic lesion without any inflammation ulceration or destruction. The clot seemed in the skin rather than on it. Klauder²⁹⁹ also saw sharply outlined pear shaped congestive areas 0.5 cm long on the forehead. These stigmata which symbolized the wounds from the crown of thorns did not have crusts.



Fig 365—St. Francis receiving the stigmata. (Painting by Francisco de Zurbarán. With permission of the Musée du Louvre, Paris.)

On Friday Theresa went into a state of ecstasy in which she seemed to endure or witness the crucifixion of Christ. During her ecstasy the stigmata became redder. The marks did not heal in the interval. In the scant secretion of the thoracic stigma and in the tears blood was found microscopically. According to reports which Ewald could not verify, and the objective truth of which he could not believe, Theresa did not eat more than a quarter host with 3 c.c. of water daily. There were no stools, but small quantities of urine containing

²⁹⁹Klauder J V. Stigmatization. Arch. Dermat. & Syph. 37: 650-6 9 1933.

acetone were secreted. The girl lost nine pounds during the ecstasy but regained her weight during the interval in spite of doing house work and other activities. Ewald and other medical observers²⁹⁰⁹ arrived at the opinion that Theresa's stigmata were genuine and not artificially produced.

The psychiatric diagnosis made not only from the ecstasies but from many other preceding manifestations was severe hysteria.

Allergic Phenomena — Purely psychogenic *urticaria* is rare^{648 2910 2911}. Psychic factors however were noticeable in 18 per cent of 170 cases⁹¹⁸ of *urticaria* and angioneurotic edema. Stokes, Kulchar and Pillsbury⁹¹⁴ in a thorough study of 100 cases estimate that psychogenous influences are the sole cause of *urticaria* in 12 per cent and a contributory cause in 68 per cent. The *urticario*genic psychogenous background seems to lie in a personality type, rather than in external impinging circumstances^{901 2915-2916}. Allergic *urticaria* may result in a conditioned reflex and persist long after the exposure to the excitement has ceased^{159 2917}. Hebra described the case of a woman who developed *urticaria* by the mere thought of some *urticariogenic* substances (Veidsen in discussion to Kohnstamm and Pinner²¹⁹).

In a well observed case⁹¹⁹ of suspected allergy to quinine *urticaria* could be produced by hypnotic suggestion of taking quinine and quinine could be taken in hypnosis without producing *urticaria* if it was suggested that it was not quinine. Kohnstamm²⁹⁰ performed the following experiment in the presence of a group of neurologists. A cross was drawn with a pencil on both arms of a subject under hypnosis. The suggestion was given that on the left side an *urticarial* wheal would develop within two hours whereas the right side would remain unaltered. After about an hour under supervision the wheal formation on the left side began. *Urticaria factitia* was excluded.

Some patients develop *urticaria* on excitement. Some are able to produce wheals in a certain spot by mental concentration on this area^{2925 899}. *Urticaria* after coitus probably belongs to this group²⁹¹¹. *Dermographism* is supposed to be common in neurotic patients²⁹²⁶. The cholinergic character of emotional *urticaria* has been thoroughly investigated. Rothman⁶⁴ considers this condition

¹ Drake J. A. Urtica is Evoked by Emotion. *Brit J Dermat* 42: 184-185, 1931.

¹⁴ Dunbar H. F. Physical and Mental Relationship in Illness. *Am J Psychiat* 21: 541-56, 1934.

¹⁵ Jarcho S. Zambecari. Life of Maria Cate (na Bro III). *Bull Hist Med* 15: 403-419, 1944.

¹⁶ Fink A. I. and Gay L. V. Review of 170 Cases of Urticaria and Angioneurotic Edema. *J Allergy* 6: 615, 1934. ¹⁷ Bull John. *Hopkins Hosp* 55: 240-250, 1934.

¹⁸ Stokes J. H., Kutchar G. V. and Pillsbury D. M. Effect on the Skin of Emotional and Nervous States. (*Urticaria*). *Arch Dermat & Syph* 31: 470-499, 1933.

¹⁹ Stokes J. H. The Personality Factor in Psychoneurotic Reactions of the Skin. *Arch Dermat & Syph* 42: 780-801, 1940.

²⁰ Bierman W. Treatment in Peripheral Vascular Disease. *Arch Phys Therapy* 21: 267-69, 1940.

²¹ Sack W. Zum Mechanismus der psychophysischen Schaltung. *Nervenzentr* 6: 57-6, 1933.

²² Kohnstamm O. a. d. P. M. Blasenbildung durch hypnotische Suggestion. *Arch. f. Dermat. u. Syph* 91: 3: 9-30, 1908.

²³ Hartmann W. A. J. Ueber das Wesen der psychischen Urticaria. *Arch. f. Dermat. u. Syph* 173: 531-536, 1936.

²⁴ Kohnstamm O. Demonstration. *Deutsch. Ztsch. f. Nervenzentr* 42: 447-448, 1911, 191.

²⁵ Hirschfeld M. Sexualpathologie. v. J. Bonn 1920. A. Marcus and E. Weber p. 58.

²⁶ Wengraf F. Fine Dermatoses post coitum. *Psychiatr. Prax* 1: 50-5, 1934.

as one of the rare cases of allergy to a physiological metabolic product namely acetylcholin. Rothman²⁸⁴ has in two out of three cases successfully desensitized patients with emotional urticaria by gradually increasing intradermal doses of acetylcholin.

Many allergic phenomena like urticaria asthma and hay fever are highly subject to psychic influence. There is much evidence accumulated that certain types of character namely the driving high strung subtle intelligent ambitious sensitive also the imbalanced and maladjusted predispose to allergy²⁷². Worry grief anxiety, fatigue stress and strains unsatisfied longing for love and affection may increase specific allergic reactions and prevent their healing¹³³. Experimental allergic wheals in persons with pronounced allergy can be increased or inhibited by hypnotic suggestions^{276 275}.

Other Psychogenic Dermadromes—Sweating—Mental stimuli e.g. mental efforts in solving an arithmetical problem pain or excitement may in some persons evoke sudden frontal axillary and especially palmar sweating^{284 29 3 276 27 7}. Apprehension of having a wet hand when shaking hands may cause palmar perspiration.

The sweat secretion generally but especially that of the palms and soles is a sensitive somatic receptor of psychic stimuli²⁷⁷. This is best demonstrated by Tarchanoff's psychogalvanic reflex (see above) which indicates increased perspiration by lowered electric resistance of the skin. The shouting of words to the test person is sufficient to evoke the reflex. *Dysidrosis* is in some cases quite subject to psychogenic factors.

Psychogenic blisters represent a more severe reaction than the changes which have been mentioned so far. The blisters may even be followed by necrosis. While great skepticism prevails with regard to the so called pemphigus hystericus of the older authors²⁷⁸ it cannot be doubted that bullae can be produced by hypnotic suggestion of a burn^{289 289 218 29 8}. Kreibich and Doswald²⁷⁹ hypnotized a physician and touched him with a stick of wood suggesting that he was being burnt with a match. After three minutes an erythema the size of a match head appeared and after three more minutes a blister of the same size was visible. Biopsy after 24 hours revealed changes identical with that of a third degree burn²⁸⁹.

Similar experiments have been repeated by many authors and with precautions which ought to rule out fakery including a plaster of Paris dressing during the experiment.

²⁷² Juckes J. H. and Beerman H. Psychosomatic Correlations in Allergic Conditions. Problems and Literature Psychosom. Med. 2, 438-455 1940.

²⁷⁷ Diehl F. and Heinichen W. Psychische Beeinflussung allergischer Reaktionen. München med. Wochenschr. 78, 1005 1009 1931.

²⁷⁸ Marcus H. and Sahlgren E. Untersuchungen über die Einwirkung der hypnotischen Suggestion auf die Funktionen des vegetativen Systems. Acta psychiat. et neurol. 11, 119-16 1936.

²⁷⁹ Kuno Y. Physiology of Human Perspiration. London 1934 J. & A. Churchill Ltd.

²⁸⁰ Kosaka T. Demonstration of Psychological Sweating by Means of Minor's Method. Jap. J. med. Sci. Trans. III Biophysics 2, 2 1931. Zbl. 42, 303.

²⁸¹ Casaccia P. Ipoevolutive infantilismi universali nelle insufficienze psichiche. Rassegna di studi psichiat. 19, 421-465 1930.

²⁸² Kreibich K. and Doswald E. C. Posthypnotische Hautphänomene. Monatsh. f. prakt. Dermat. 42, 634-640 1906.

Herpes simplex and especially *herpes genitalis* is subject to psychogenic influences such as guilt and fear of venereal infection after extramarital coitus

Pruritus is highly susceptible to psychogenic influences⁹⁹³ Every dermatologist knows of patients with lichen ruber and lichen Vidal chronic eczema psoriasis and prurigo whose skin disease is more itchy on excitement and calms down when the patient does However while mental impulses are very common contributory factors purely psychogenic pruritus is rare^{1116 930}

In order to prove the existence of completely psychogenic pruritus Sack induced pruritus by hypnotic suggestion in the locally anesthetized finger of a patient Pruritus may be a symptom in endogenous and reactive depressions

The sexual background of anal and vulvar pruritus has frequently been analyzed^{994 29 3} Many psychoanalysts believe that the pruritic seizures and the relief of tension achieved by violent scratching are sexual or homosexual equivalents These relations seem to have been overemphasized⁹⁹⁵

Psychogenic eczema is illustrated by the following case⁹⁹⁶ Psychoanalysis traced the origin of an eczema on the buttocks to a nauseating dream in which the patient had seen himself covered with feces as high as the eczema indicated Psychoanalysis cured the patient^{997 1933}

Sudden *blanching of the hair* caused by terrifying experiences is still controversial The two leading American textbooks of dermatology arrive at opposite opinions Ormsby and Montgomery⁶³³ admit it as a rare probability of clinical experience while Sutton and Sutton⁶⁴⁷ explain it as the result of the removal of cosmetic coloration or of the application of a bleach The main argument against it is the lack of greater numbers of observation in both World Wars with millions of terrifying occasions The number of well documented cases⁹⁹⁸ seems too small to rule out the possible errors especially that of having been gray before the event⁹⁹⁹ The physiological possibility of a sudden graying must be admitted Landois' old theory that in such cases the pigment is hidden by reflecting gas bubbles has found considerable supporting evidence¹⁰⁰⁰

Mental stress strain and shock probably play an important role as a trigger factor in *alopecia areata*¹⁰⁰¹

In the opinion of the *psychoanalysts* psychogenic dermatoses always have a meaning¹⁰⁰² In some instances they symbolize their origin as in the case of ecchymoses after seeing blood¹⁰⁰³ in the mystic stigmas or in the cases of psoriasis provoked by the terrifying and prolonged sight of decomposing corpses in

⁹⁹³Pearson G H J Some Psychological Aspects of Inflammatory Skin Lesions *Psychosomatic Med* 2 29-33 1910

⁹⁹⁴Klauder J A Psychogenic Aspects of Skin Diseases *J Nerv Dis* 81 49-273 1936
⁹⁹⁵Bruchneier A Psychogene (on irogene) Krankheitsfälle *Arch F Kinderh* 98 51-55 1933

⁹⁹⁶Rogerson E H Psychological Factors in Skin Diseases *Practitioner* 142 17-35 1939
⁹⁹⁷Vigolo-Lutati G Canicizie precoce e psicopatie di guerra *Policlinico (sez prat)* 23 680 1918

⁹⁹⁸Ingram J T Baldness Causes and Treatment *Med Press* 209 41-44 1943

⁹⁹⁹Schulder P Psychophysiology of the Skin *Arch Dermat & Syph* 39 843-858 1931

front of trenches where the patient fought.^{227 228} In some of these cases cure has been accomplished by hypnotic suggestion. Schilder²²⁸ expresses the opinion without proving it that anal itching is an expression of sadomasochistic tendencies blushing manifests a narcissistic attitude and blisters and hemorrhages are closely related to a hysteriform attitude with a strong infantile Oedipus complex.

While classic psychoanalysis has found but little acclaim among the dermatologists, the importance of tensions conflicts emotions overwork fatigue shock worries insomnia inferiorities frustrations and other psychic factors on the origin and course of dermatoses has been emphasized time and again.

This has been done in the most human practical and convincing way by Stokes.²²⁹ Purely psychogenic dermatoses are rare and do not develop typical morphological pictures with the exception of the self inflicted dermatoses.

Yet it is exceedingly common that the psyche influences the course of a disease for better or worse psoriasis lichen planus²³⁰ chronic eczema lichen Vidal dermatitis herpetiformis and alopecia ureta furnish the best examples (see also Obermeyer^{230a}). The psychosomatic relationship of atopic dermatitis is particularly striking.²³¹ These patients are often highly intelligent aggressive and ambitious as well as tense and fidgety. It is more likely that their nervousness is primary rather than due to their itching and disfigurement which of course may also leave its mark. Their behaviour and character are quite different from other suffering or disfigured people. Family conflicts are often in the background of such cases not infrequently caused by arguments on the treatment or diet. This was strikingly illustrated in one of the author's cases. An intelligent boy of 13 with severe atopic eczema improved immediately after the mother was advised to discontinue all discussions and arguments on his diet which had disturbed almost every meal. Later the trouble recurred on other conflicts. Overattention as in only child or resentment because of sibling rivalry, frustration and parental rejection may also occasionally express themselves in more intensive itching and scratching and consequent impairment. The children soon learn to use their ailment as a weapon.^{42 231}

In this group probably belongs *acne urticata*.²³¹ In this condition the lesions which may occur on the face or anywhere on the body are at first wheals or papules which itch intensely and become infiltrated and excoriated under constant scratching. They disappear after several weeks leaving a pigmented spot. The eruptions may keep appearing for years. In some of these cases a psychogenic background is obvious. In one of the author's cases the disease broke out in a young woman after the husband had gone overseas and eased up on the news

²²⁷Buntema in O. Leyh and A. von Hautsymptom u. Ztschr. f. d. ges. Neurol. u. Psychiat. 88: 589-600 1934.

²²⁸Hunneemann O. i. b. psychogen. Hautveränderungen. Psychotherapeut. Prax. 1: 3-36 1934.

²²⁹Stokes J. H. Functional Neuroses as Complications of Organic Diseases. An Office Technique Approach. With Special Reference to the Neurodermatoses. J. A. M. A. 103: 1007-1013 1935.

²³⁰Goeckerman W. H. The Relationship of Emotions and Cutaneous Lesions. Med. Clin. North America 14: 645-647 1930.

^{230a}Rogerson C. H. Psychotherapy and the Asthma Eczema-Prurigo Complex in Children. Brit. J. Dermat. 45: 304-311 1934.

²³¹Kaposi M. Lebererleid. ungewöhnliche Formen von Acne (Folliculitis). Arch. f. Dermat. u. Syph. 25: 57-66 1895.

that he was out of the danger zone. The patient was an intelligent high strung person of a type commonly encountered in atopic dermatitis to which the condition seems to be related. Acne urticata also may be seen in atopic dermatitis.

Burning tongue is highly susceptible to psychic influence. In this condition the impulse may act through the sensitive psychosomatic mechanism of the gastric acidity. Becker and Obermayer¹³⁰ call *neuronychia* nail changes which either consist of separation of the nail from the bed or of superficial pitting, thickening, thinning or splitting. The authors saw the condition associated with neurodermatitis or as the only somatic manifestation of nervous instability and exhaustion.

Hysteria—Conscious or subconscious production of symptoms, the main feature of hysteria, leads into the field of the self inflicted dermatoses (neurotic excoriations, dermatitis factitia). The variations of clinical appearance are innumerable but there are some features which are often encountered. The feigned



FIG 366 — Acne ex oris. The scabs are caused by ultraviolet light.

lesions are usually within the reach of hands, preferably of the right hand. The artefacts and their scars often have a strange angular, round or linear, unnatural appearance which arouses the suspicion of the experienced dermatologist.¹³¹ Sometimes traces of a chemical used in the production of lesions can be found in the surroundings or on the scab. If the circumstances permit the application of a sealed occlusive dressing, especially with plaster of Paris is advisable. If healing of the suspected lesions of long standing follows, further evidence of self infliction is given.

¹³⁰Becker S W and Obermayer M E. Modern Dermatology and Syphilology. Philad. Phila. 1943. J B Lippincott Co.

¹³¹Genear F F and Shellow H. Neurotic Excoriations. Arch. Dermat. & Syph. 46: 5 4-25 1942.

However one should keep in mind that the typical pathomimic changes represent only a minority among the great variety of entirely or partially self inflicted lesions. More commonly a spontaneous dermatosis like acne or a patch of eczema is kept going by picking scratching or treating. Excoriated acne is found not only in young girls (Brocq's *acné excorié des jeunes filles*) but also in middle aged women.

The psychology of self induced eruptions ^{853 2894 897 900 2923} ranges from the sometimes criminal, but simple and mentally normal cases of military or civilian malingerer to more complicated and often decidedly pathological states of mind. In one of these cases (Dieulafoy after Simon²⁸⁹²) recurrent deep ulcerations of the hands and arms led to various major operations and finally to the amputation of one arm. The patient would not have hesitated to have his other arm amputated if the right diagnosis had not been made. Under some grilling the patient admitted that he had placed pieces of potassium hydroxide on the



Fig 367. Trichotillomania

mantlepiece and then put his arm on it. Similar cases are on record. The most plausible motivation is an escape into disease. The suffering arouses sympathy and attention which the patient is craving. Strangely enough the motivation may also be lack of erotic attention. A woman may try to get the sympathy and with it the love of her husband. This might be called the 'poor little dear' motivation. Psychoanalysis may also detect underlying unconscious motives.



Fig 368 —Trichotillomania



Fig 369 —Trichotillomania. (Courtesy Division of Dermatology Department of Medicine University of Chicago)

of guilt and punishment^{2900 2945} In this group belong the patients who keep pyodermic lesions on the face open with tweezers

Some of these patients are *feeble-minded* who without any purpose follow an exaggerated urge to remove all little follicular plugs to dig after or pull out ingrown hairs and to scratch every scale on the scalp

The cases of neurotic excoriations lead to the true cutaneous *manias and phobias* There is the urge to rub the hair between the fingers to bite the nails to break hairs or to pull the hair out (trichotillomania) This latter condition



Fig. 370 — Neurotic excoriations

usually found in children is often combined with anomalies like enuresis and mental retardation^{2946 2947} paranoia²⁹⁴⁸ or postencephalitic state²⁹⁴⁹ It has also been observed as a psychic epidemic in institutions (Haldin Davis in discussion to O Donovan²⁹⁵⁰) Transitory cases without apparent deeper significance are also known^{29 1} Apparently unique is a case of plucking the mustache²⁹⁵²

²⁹⁴⁵ Casazza H. Sull'importanza di fattori psichici in dermatologia (a proposito di autolesioni cutanee in isteriche) Boll d Soc m d-chir Pavia 44 115 167 1930 Zbl 35 261

²⁹⁴⁶ Juhl S. Ueber Trichotillomanie Dermat Ztschr 58 236 239 1930

²⁹⁴⁷ Tarozzi G. L. Su di un caso di Trichotillomania Pediatria prat 10 393-407 1933

²⁹⁴⁸ Chashi K. Ein Fall von Trichotillomania Jap J Dermat 32 70 193. Zbl 42 619

²⁹⁴⁹ Perantoni Satta M. Considerazioni cliniche su un caso di pseudotrichotillomania Dermo-sifillografo 6 449 460 1931

²⁹⁵⁰ O Donovan W. J. Infantile Trichotillomania Proc Roy Soc Med 26 836-838 1933

²⁹⁵¹ Jolley A. Hair Plucking Am J Dis Child 51 336-337 1936

²⁹⁵² Photinos I. B. Aetiology der Trichotillomanie Dermat Ztschr 61 239 240 1931

Cutaneous phobias and *hypochondriac complaints* which appear suddenly should be reason to search for an underlying psychosis^{373 393} or addiction to morphine or cocaine.

Patients who persistently bring little follicular plugs scales or woolen fibers wrapped in paper or kept in a box to convince the doctor that they have worms or insects in their skin that they feel them creeping clicking digging and that they have to crush them between their fingers have delusions and belong to a psychiatrist^{384 394}. Such delusions of parasites or dermatozoa may occur in the toxic psychoses in dementia praecox in involutional melancholia and in paranoia and paranoid conditions. The prognosis is poor. Only about 10 per cent of the reported 51 cases have been cured³⁹⁵. A greater significance may be attached to the severe cases of patients who wash their hands excessively avoid touching a door handle and have constant fear of body odor or of being dirty or of blushing.



Fig. 371.—Neurotic nail biting.

Tattooing while normally a badge of membership to certain groups (sailors) or just being a fad may also express psychopathological conditions^{317 318} with an erotic homosexual or criminal background. During the second World War the rejection rate for tattooed men was almost 50 per cent greater than for nontattooed men and 58 per cent of all rejections among tattooed men were on the basis of neuropsychiatric disability in contrast to only 38 per cent among the nontattooed³¹⁹. These military statistics are according to the authors.

³¹³Graham Little F. Neurotic E correlation. Irer Roy Soc Med 26 646 1931

³¹⁴Fekhom h. A. Præ nll D matozoonw hn Acta p; hlat n urol 12 277 1934

³¹⁵Wilson J W and Miller H F. D lesion of Parasitoid (Acarophobia) Arch Dermat & Syph 39 57 1946

³¹⁶Wright H. S. Psychosomatic Aspects of Dermatoses Clinics III 711 727 1941

³¹⁷Bromberg W. Psychologic Motives in Tattooing Arch Dermat & Syph 29 545 592 1934

³¹⁸Parry A. T. (too New York 1933 Simon & Schust Inc

³¹⁹Land J and Hohn H M. Tattooing Amer g lectures (lay biatric significance) Am J Psychiat 100 326-327 1943

based on numbers large enough to be valid though exact absolute figures are not given. Among the men rejected for antisocial inclinations 68 per cent had multiple tattoos.

Psychotherapy of Dermatoses — If a psychic factor causes or as it more frequently happens influences the course of a skin disease, the removal of this cause should be tried. The office technique approach^{2901 2929} may be learned depending on the interest and aptitude of the dermatologist but at the present stage of our training the aid of a trained psychiatrist should be sought^{2941 2960} to the greater advantage of both parties.

Hypnosis has occasionally been successful in the treatment of psoriasis²⁹⁶¹ and eczema.²⁹⁶⁶

The *psychotherapy of juvenile as well as ordinary warts* has been practiced by lay healers for centuries under many forms.²⁹⁶² Bloch²⁹⁶⁴ stimulated scientific interest in the matter by healing 44 per cent of verrucae vulgares and 88 per cent of verrucae planae by verbal suggestion painting with color and turning on a buzzing electric motor. No consensus exists about the post hoc ergo propter hoc but it is the impression of many experienced dermatologists that suggestion therapy is effective in a varying percentage. Some cases are very impressive.^{2963 2965} Memmesheimer and Eisenlohr²⁹⁶⁶ treated 70 out of 140 cases of ordinary warts by suggestion and left the other 70 untreated. There was no significant difference in the percentage of cures. The cure of condylomata acuminata by suggestion has been reported by Bonjour.²⁹⁶⁷

²⁹⁶⁰ Weiss E and English O S. *Psychosomatic Medicine* Philadelphia 1943 W B Saunders Co

²⁹⁶¹ Wisch J M. Anwendung der Hypnose bei Psoriasis. *Dermat Wechnschr* 100 731 736 1935

²⁹⁶² Dubnikov E. Zur Frage der Behandlung des Ekzems nervösen Ursprunges durch Hypnotismus. *Vruch delo* 18 634-636 1937 Zbl 46 4 0

²⁹⁶³ Zwilek H G. Idiogene 14 of Warts Disappearing Without Topical Medication. *Arch Dermat & Syph* 28 509 521 1932

²⁹⁶⁴ Bloch H. Ueber die Heilung der Warzen durch Suggestion. *Illust Wechnschr* 8 71 73 0 1927

²⁹⁶⁵ Dohl G. Heilung der Warzen durch Suggestion. *Jap J Dermat* 20 29 1930 Zbl 26 318

²⁹⁶⁶ Memmesheimer A M and Eisenlohr E. Suggestivbehandlung der Warzen. *Dermat Ztschr* 62 63-65 1931

²⁹⁶⁷ Bonjour J. La guérison des condylomes par la suggestion. *Pr se méd* 116 616 10 9

CHAPTER XLI

DISORDERS OF THE GASTROINTESTINAL TRACT

The various sections of the gastrointestinal tract are highly interdependent. Gastric hyperacidity for example may lead to increased motility of the small intestine causing the chyme to be rushed to the colon before the digestion in the bowel is completed. Thus toxic intermediate products may be reabsorbed and transported through the portal system to the liver where detoxification may take place provided the liver functions are unimpaired. A fraction however may enter the circulation directly through the vena cava. Deficiency of the antiseptic hydrochloric acid results in incomplete digestion and partial retention of the food. Another important consequence is the change of the intestinal bacterial flora with ensuing putrefaction of large amounts of mucus. Local inflammatory lesions may change the permeability of the mucous membranes, thus permitting the passage of toxic and allergenic substances^{959 970} through the intestinal barrier though much work remains to be done to *prove* the pathogenesis of skin changes by pathological absorption.

Dermadromes—Yet cutaneous symptoms arise only in a small fraction of gastrointestinal disorders. No obligatory dermatome is known in connection with gastrointestinal diseases but several dermatoses occur occasionally. The percentage of skin diseases in large series of gastrointestinal cases is small. Even the conditions commonly ascribed to gastrointestinal causes such as pruritus, urticaria and eczema were recorded in less than one per cent of 5000 different gastrointestinal cases⁹⁷¹. Among 595 gastrointestinal cases⁹⁷² rosacea was observed in 3.5 per cent⁹⁷³. In some groups e.g. peptic ulcer or colitis the incidence of dermatoses is higher. The percentages of varied gastrointestinal disorders in patients suffering from chronic eczema, neurodermatitis, urticaria, pruritus, acne, rosacea and acne urticata are significant. The possibility of a gastrointestinal cause should be kept in mind in persistent and unexplained cases of these dermatoses.

Mouth—While the oral cavity is very often concomitantly affected by dermatoses or takes part in manifestations of internal disorders a primary mouth disease only rarely causes dermatomes. In this connection one should remember the role the teeth and tonsils play in focal infections. Perlèche may be caused by malocclusion and ill fitting or old dentures and salivation^{974 975}.

⁹⁵⁹ Urbach F. Magen-Darmtrakt und Haut. Wien med. Wchnschr. 1937 I 20: 91-3, 103-6.
⁹⁶⁰ Ling R. Die endogene Natur mancher Hautkrankheiten. Verh. d. Ges. f. Verd. u. Stoffw. 1936 101: 105-13.
⁹⁷¹ Poissonier O. Verdauungsstörungen und Dermatosen. Wien klin. Wchnschr. 1926 39: 568-569.
⁹⁷² Basler A. The entero-dermal syndrome. Lrol. & Cutan. Rev. 35: 504-509, 1931.
⁹⁷³ Ryn A. Rosacea. Zbl. 52: 462, 1936.
⁹⁷⁴ Epstein N. Gastric Analis in Acne Rosacea. California & West Med. 35: 115-116, 1931.
⁹⁷⁵ Freund H. Die Fäkalien bei Erwachsenen. Intestinalmuskulose und ihre symptomatische Bedeutung. Arch. f. Dermat. u. Syph. 164: 614-622, 1933.

The shape of the lips and the tendency to form persistent wrinkles or folds at the angles of the mouth may favor localized mycotic or bacterial infection particularly in diabetics. The author saw a mother of 75 years and her son of 52 years who both had a peculiarly hanging upper lip as a familial trait suffering from almost incurable perleche. Persisting eczema of the face and cheilitis even severe papillomatous forms may occasionally be caused by pyorrhea and oral ulcerations²⁹⁷⁵. Salivation especially during the night may well cause dermatitis which according to the sleeping habits of the patient may be unilateral¹¹⁸ or bilateral.

Diseases of the Stomach

A great number of investigators have tried to correlate the status of *gastric acidity* with skin disease (Spiethoff²⁹⁷⁶ and later also investigations of his pupils Ehrmann^{2977 298}, Lejhanec after Ottenstein⁹). The results have shown that a general tendency to lowered gastric acidity exists in pruritus⁹⁷⁸ eczema neurodermatitis²⁹⁷⁹ chronic urticaria rosacea^{297 973 2980 981} seborrheic



Fig. 372 — Chronic perleche caused by ill fitting dentures

²⁹⁷⁵Dongen K. van Zusammenhang von Krankheiten im Munde und im übrigen Körper. Ztsch. f. Stomatol. 32 1109 1110 1934 Zbl. 50 162

²⁹⁷⁶Spiethoff H. Magenstörung n bei Hautkrankheiten. München med. Wchnschr. 59 991 191

²⁹⁷⁷Ehrmann G. Ueber den Zusammenhang zwischen Verdauungsstörungen und Dermatosen. Wien klin. Wchnschr. 39 756 757 1916

²⁹⁷⁸Ehrmann S. Ueber den Zusammenhang der Neurodermitis mit Erkrankung und Verdauungsstörungen und Störungen der inneren Sekretion. Arch. f. Dermat. u. Syph. 138 345 360 1932

²⁹⁷⁹Urbach E. Roiginologische und klinische Befunde am Magen-Darmtrakt bei Ekzemen und ihre Bedeutung für ein kausales Theaple. Arch. f. Dermat. u. Syph. 142 941 1923

²⁹⁸⁰Eastwood M. R. Gastric Secretion and Other Digestive Factors in Rosacea. Brit. J. Dermat. 40 101 104 148 167 1919

²⁹⁸¹Stokess J. H. and Pillsbury D. M. Dermatoses and Gastric Disturbances. Arch. Dermat. & Syph. 22 962 993 1930

²⁹⁸²Piper H. G. Magensekretionstörung und Haut. Dermat. Wchnschr. 110 317 323 1940

²⁹⁸³Brown W. H. Smith M. G. and McLachlan A. H. Fractional Gastric Analysis in Diseases of the Skin. 316 Cases. Special Reference to Rosacea. Brit. J. Dermat. 47 181 190 193

dermatitis moniliasis in diabetes kraurosis vulvae⁹⁸⁴ and some other dermatoses⁹⁸⁵ Urbach²⁸ and also Ehrmann⁹⁷⁸ emphasized the frequent (22 per cent) finding of hyperperistalsis along with anacidity in cases of neurodermitis

Great and almost unexplainable discrepancies exist among the many reports⁹⁸⁶⁻⁹⁸⁸ (also Johansen after Ottenstein⁹)

Newer investigations partly allowing for the physiological subacidity of the higher age classes²⁸⁸⁹⁻²⁹⁰ have confirmed though not unanimously⁹⁹¹ that the gastric acidity tends to be subnormal in chronic inflammatory dermatoses²⁹⁰³ Lejhanec after Ottenstein⁹ even if the involved skin area is relatively small⁹⁸⁹

The observations differ in the acute dermatoses and in the acute exacerbations of chronic skin diseases: Such states seem more likely to coincide with a tendency to hyperacidity. This would be in line with observations of hyperacidity after mechanical irritation radiation with ultra violet light⁹⁹⁰⁻⁹⁹¹ X ray⁹⁹⁰ skin irritations with mustard plaster⁹⁹ and extensive burns (Diehl Jr after Urbach⁹⁶¹) Very severe burns however may cause anacidity (Geber after Urbach⁹⁶¹) The serum of blisters from burns or freezing with CO snow contains a histamine like substance⁹⁹⁰ It is therefore suggestive to explain the hyperacidity as the result of release of histamine from the inflamed skin²⁹⁰³⁻⁹⁹³ More difficult to explain is the subacidity in a relatively small lesion In this case skin and stomach disorders are likely to be caused by a common factor The individual constitution also has a great influence on the acidity²⁹³ The favorable effect of HCl therapy on some skin diseases would seem to prove that the subacidity is the cause of the skin disease Unfortunately the value of this often recommended treatment is not generally confirmed⁹⁹⁵

Elimination of toxic substances from the skin into the stomach may be the cause for gastric ulcers in extensive burns (Richl Jr after Urbach⁹⁶¹) though thirty autopsy reports⁹⁹⁴ do not mention such lesions Little can be said as to whether ulcers associated with dermatitis²⁹²⁻²⁹ are due to eczema or

⁹⁸⁴Gross P Non Pellagrous Eruptive Duodenal Deficiency of Vitamin B Compl Arch Dermat & Syph 42 64-53 1941

⁹⁸⁵Ayre S J Gastric Secretion in Poliosis Erythematosa and Dermatitis Herpetiformis Arch Dermat & Syph 20 854-59 1929

⁹⁸⁶Wall S Histologische Aetiologie der Ekzeme Grundlege 63 111 113 19 1 Zbl 2 269

⁹⁸⁷Stokes J H and Sherman H Effect on the Skin of Emotional and Nervous States IV The Rosacea Complex Arch Dermat & Syph 28 479-491 1931

⁹⁸⁸Bergman O Koloidale und vaskuläre Ulcerationen und Hautkrankheiten Wien klin Wchnchr 47 915-919 1934

⁹⁸⁹Loe H and von H Verkinigung der Magensekretion als Ursache sondern als Folge von Hautkrankheiten Mbl f. med. Wchnchr 1937 II 1456 1459

⁹⁹⁰Voss J Relation between Disorders of Secretion and Skin Diseases Wchnchr 211 686 694 1910

⁹⁹¹Diehl J Die Wirkung der Ultra- und Röntgenstrahlung auf die Magensaftsekretion Naunyn-Schmiedberg's Arch 189 367-371 1931

⁹⁹²Anton M Sulla modificazione della secrezione gastrica per effetto della timolazina sulla regione epigastrica Arch Ital di mal di app 119 1 194 197 193 211 42 194

⁹⁹³Desaux A and Antol E Relations entre la peau et le tube digestif Verb D f. r. at l. r. Dermat 1 105-126 193 also 2 3 6 1936 Zbl 53 4 and 58 99

⁹⁹⁴Colbrook L and others Histology of Burns a 1 Scoll Medical Research (1 11 11 11 Report No 12 Lond 1944 His Majesty Stationery Office

⁹⁹⁵Lortat-Jacob L Skin Diseases and Functional Disturbances of Various Organs 1929-1930 1923

vice versa, or whether ulcers and dermatosis have a common cause. The impression prevails that there exists a more than coincidental relationship.

The advent of *gastroscopy* has recently revealed some relations which were not known before. The gastric mucosa takes part in cutaneous lichen planus in about 20 per cent of the cases. Urticaria may show in the stomach and skin simultaneously.^{2998, 2997} Vesicular gastritis has been seen to accompany some cases of acute vesicular dermatitis. In stationary eczema the gastric mucosa has usually been found in normal condition. Gastritis of varying degrees of severity was present in 18 out of 19 patients with rosacea, whereas among the 15 control cases of other dermatoses only 4 patients showed evidence of gastritis.²⁹⁹⁸ In 2 patients coincidental improvement of both gastritis and rosacea could be visualized by the gastroscope.

Urbach²⁹⁹⁸ suggests that the dysfunction of the gastric mucosa may lead to increased permeability for substances from incompletely digested food which normally cannot be absorbed. This may cause allergization with cutaneous symptoms like urticaria, eczema, pruritus, urticaria papulosa, etc. Abnormal absorption of allergens may also occur from gastric or duodenal ulcers.

The validity of the old observations regarding the *tongue in gastric conditions* has recently been checked by Oatway and Middleton.²⁹⁹⁹

The surface of the tongue reflects the acidity of the stomach quite reliably. In *hyperchlorhydria* and also in peptic ulcer the tongue is rarely smooth but often scrotal or coated. Superficial defects may appear in the fur of the posterior tongue, a lesion which has been related to gastric ulcer.³⁰⁰⁰ In *achlorhydria* or subacidity smoothness of the tongue is common and still more so when achlorhydria is combined with anemia. The patients often complain of soreness of the tongue and a dry throat though objective changes are frequently absent.

The Small Intestine

Pain, distention, audible peristaltic noises, nausea, vomiting, diarrhea and constipation are the primary symptoms which characterize disorders of the small bowel (Ingelfinger in Portis³⁰⁰¹).

Besides the inspection of the stools, chemical, microscopic, bacteriological and helminthological examinations should be carried out. Enteritis without any involvement of other parts of the tract is relatively rare.

Dermadromes — *Pruritus*³⁰⁰⁶ urticaria and eczema have been frequently found to accompany enteritis. The connection was usually demonstrated by

²⁹⁹⁸Chevallier J and Moutier F. L'estomac des eczémateux. Verh 9 Internat Congr Dermat 2: 107-112, 1936. Zbl 51: 99.

²⁹⁹⁷Chevallier P and Moutier F. L'estomac dans l'eczéma vulgaire à début et à p. éducation antilachrye. Nutrition 6: 19-31, 1936. Zbl 54: 594.

²⁹⁹⁸Usher H. Gastroscopic Observations in Rosacea. Arch Dermat & Syph 41: 251-255, 1941.

²⁹⁹⁹Oatway W & Jr and Middleton W S. Correlation of Lingual Change With Other Clinical Data. Arch Int M 1: 49: 860-876, 1932.

³⁰⁰⁰Glaessner K. Ueber die Ursache der Verdauungsstörungen. 51: 63-73, 1932.

³⁰⁰¹Portis C A. Diseases of the Digestive System. Philadelphia 1944. Lea & Febiger.

the effect of dietary measures^{305 370 100} or intestinal treatment with activated charcoal³⁰⁰³ after protracted topical therapy alone had failed. Protein putrefaction and carbohydrate fermentation could frequently be demonstrated in the feces in eczema especially perianal eczema, acne, urticaria, pruritus³⁰⁰⁴ and in infantile eczema³⁰⁰. The bacterial flora produces porphyrins the light sensitizing property of which is well known.

Urinary indoxyl = sign of intestinal putrefaction was not found increased in 42 cases of eczema³⁰⁰⁶. Vaccines derived from fecal bacteria have been found useful in the treatment of some dermatoses but this method has not found much acclaim from dermatologists. Achylia gastrica and enteritis may be followed by the accumulation of feces and mucus in the cecum with subsequent inflammation. This typical syndrome of *typhilitis* (cectis)^{970 3007} with dull pain in the ileocecal region is often mistaken for appendicitis. Neurodermatitis, lichen urticatus, urticaria and eczema have quite frequently been found associated with typhilitis. These dermatoses disappeared after treatment of the typhilitis with HCl and a diet free of irritating cellulose fibers^{2903 2376 97}. Creosote has been advocated as an intestinal disinfectant.

Sprue — Sprue is a disease of the small intestine characterized by functional motor disorders and impaired absorption of foods particularly fats' (Ingelfinger in Portis³⁰⁰¹). The cause is not known but a nutritional deficiency probably resulting from a protracted diet deficient in vitamin B complex and in proteins and too rich in carbohydrates is suspected. Manson Bahr³⁰⁰⁸ emphasizes the importance of preceding intestinal infection. Progressive weakness, mental depression, severe macrocytic anemia, muscular wasting and emaciation are typical of fully developed cases³⁰⁰⁹. In contrast to pernicious anemia the stomach usually contains free hydrochloric acid. The most important features are diarrhea with pale greasy, foul smelling, unformed watery stools, cramps and distention. Secondary deficiencies develop particularly of the fat soluble vitamins. The characteristic pathologic changes are atrophy of the fat soluble vitamin and extreme depletion of the fat reserves of the body. Not too far advanced cases respond to liver therapy in a way similar to pernicious anemia.

The disease is common in some tropical countries particularly India and China but as is now known a probably identical disease is not rare in the temperate zones of Europe and America. The infantile form is known as celiac disease.

- ³⁰⁰²Altken R. The Reaction of the Stools and Its Relation to Diseases of the Skin. *Brit J Dermat* 13 17 1919.
³⁰⁰³Callag J. De matitis Follicularis. Hypo keratosis. Prurigo a Circumscripta—Successful Treatment With Charcoal. *Zbl* 25 4-3 1931.
³⁰⁰⁴Schwartz H J. Association of Intestinal Indigestion With Various Dermatoses. *Arch. Dermat* & Syph 11 6 674 19 6.
³⁰⁰⁵Montaur H and Coul're A. Les modifications chimiques des sels au cours de l'évolution de l'eczéma chez le nourrisson. *Bull Acad Med Paris III* 104 91 93 19 0.
³⁰⁰⁶Engelman E H and Bahr J G. Etwelsstühle und Hautkrankheiten. *Nederl tijdsch v geneesk* 1930 I-1316-1331. *Zbl* 25 40.
³⁰⁰⁷Porges O. Leber und Darm bei Dünndarmkatarrh und Dermatosen. *Nederl tijdsch Wehnach* 1932 I 251 23.
³⁰⁰⁸Manson Bahr F and Willoughby H. Sprue. 200 Cases. *Quart J Med* 23 11-42 1930.
³⁰⁰⁹Hanes F M. Sprue in H A Chittus. *Oxford Medicine* vol. 5 New York 1939. Oxford University Press p 631.

Dermadromes—The long known³⁰¹⁰ importance of the mucocutaneous manifestations of the sprue syndrome has recently been re emphasized by Kaufman and Smith³⁰¹¹. Glossitis probably reflecting similar changes in the intestinal tract is very common and if combined with characteristic diarrhea is suggestive of the disease.



Fig 373 —Sprue. Atrophic glossitis and facial pigmentation. (From Manson Bahr Sir Philip Quart J Med)

Stomatitis and glossitis occur in more than 75 per cent of the cases^{3012 3013} often preceding anemias³⁰¹⁴. The tongue changes involve at first the edges and the tip later the entire surface starting with aphthae or minute shallow ulcers along the edges³⁰¹⁵ and inflammation of the fungiform papillae. The sense of taste is often lost in acute sprue and salivation is increased. The glossitis may precede the diarrhea. The tongue is extremely tender especially in the presence

³⁰¹⁰Bahr P H. A Report on Researches on Sprue in Ceylon 1912 1914 London 1915 Cambridge University Press

³⁰¹¹Kaufman W H and Smith D C. Cutaneous Changes in Sprue Syndrome JAMA 121 168 173 1943

³⁰¹²Thaysen T E H. Ten Cases of Idiopathic Steatorrhea. Quat J Med 4 350 395 1935

³⁰¹³Low M C. Sprue 150 Cases. Quart J Med 21 53 634 1929



Fig 374 —Sprue Chloasma perioral (From Kaufman W H and Smith D H
J A M A 1913)

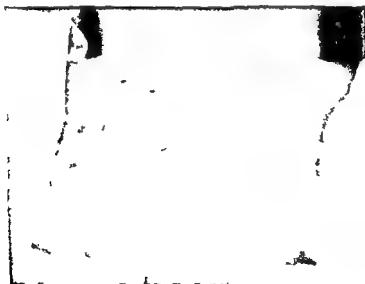


Fig 375 —Sprue Pigmentation of abdomen (From Manson Bah Sir Philip Quaint J Med)

of aphthous ulcers. There often are indentations of the edges of the tongue caused by the teeth. Atrophy of the tongue with complete disappearance of the fungiform papillae occurs later^{3008 3010}. In such cases the tongue is narrow and pointed.

The fully developed picture shows absence of the filiform papillae with the fungiform papillae remaining as prominent shiny sometimes hemorrhagic points^{3011 3012}.

Painful rhagades may cut the tongue in both directions. Fissuring of the angles of the mouth is also common. Buccal and infralingual aphthae have been found varying from 22.5 to 67 per cent in large series^{3009 3013}.

The skin is pale, dry, flabby, grayish yellow but not icteric. Large freckles and symmetric chlorasma like patchy or diffuse pigmentations have been recorded. Even Addison's disease is sometimes suggested. Some degree of pathologic pigmentation was seen in the majority of the well-observed cases^{3008 3011 3012}. Pellagroid pigmented patches on the dorsa of the hands have also been seen^{3011 3013}. The pigment was found iron free, thus probably being melanin. The pigmentations in sprue seem to improve with treatment³⁰⁰⁹ of the disease.

*Intestinal polyposis may be associated with jet black melanin pigmentation in dots and spots about the mouth, the lips and over the hands*⁶⁴⁸. Similar pigmentations have been seen in *gastrojejunal colic fistula*, *tuberculosis of the ileum*, *celiac disease*. Jeghers⁶⁴⁸ believes that pigmentation without pellagra is more pronounced in diseases of the small intestine than in disorders of the colon. Urbach¹⁶ suggests that the oxidation of phenol substances possibly also of skatol may lead to excessive melanin formation though no proof for this probability has been offered as yet.

Ulcerative Colitis—Nonspecific ulcerative colitis is in about 2 to 3 per cent complicated by skin lesions^{3014 3015}. Most troublesome and conspicuous are ulcerations which may occur³⁰¹⁶ on the lower legs. They increase rapidly in size after taking on a kidney shape. They are painful and quite deep but the healing tendency is marked. The appearance and disappearance of the skin lesions may reflect the course but not the extent of the colitis^{59 3014 3017}.

The author observed a case of ulcerative colitis in a woman who after an unhappy married life went through the excitement of a divorce. The periods of worry and excitement not only produced acute attacks of colitis but also new and severe ulcerations of the legs.

⁶⁴⁸Jeghers J. A.: Complications and sequelae of Chronic Ulcerative Colitis. *Ann. Int. Med.* 3: 335-352, 1929.

³⁰¹¹Jeghers J. A.: Present Status of Colitis and Regional Enteritis. *Bull. New York Acad. Med.* 20: 33-35, 1914.

³⁰¹⁴Bruntling L. A., Goeckelman W. H. and O'Leary J. A.: Erythema Gangrenosum. *Arch. Dermat. & Syph.* 22: 655-657, 1930.

³⁰¹⁷Jones C. M.: Peripheral Complications of Ulcerative Colitis. *Med. Clin. North Am.* 14: 919-925, 1933.

Pigmentations of the face and body, also of the dorsa of the hands may occasionally take on the characteristics of sprue or pellagra. Thickening and distal loosening of the nails may occur.³⁰¹⁸



Fig. 376.—Leg ulcers in ulcerative colitis. (Courtesy Dr. J. I. Jackson.)

Dryness and scaliness, follicular keratosis, symmetrical atrophy, pigmentations, various erythemas and cheilitis have been observed, and at least in part have been interpreted as avitaminoses.^{3081, 3014, 3017, 3019}

Tongue and buccal changes occurred in 60 per cent of Wickes's³⁰¹⁹ 75 cases. They may correspond to those in sprue. There was accentuation of the papillae fungiformes, strawberry tongue in the earlier stages and smooth atrophy later. In severe cases a stomatitis indistinguishable from that in pellagra may develop.

³⁰¹⁸ Miller, J. J.: *Procedura Chirurgica*. Onychophos and Onycholysis. With Colitis. *Arch. Dermat. & Syph.* 40: 541-543, 1930.

³⁰¹⁹ Wickes, T. T.: Ulcerative Colitis. II. The Factor of Efficiency States. *J. A. M. A.* 104: 1-18, 1935.

Whitfield¹⁰⁶ called "dermatitis colonica" a parapsoriasis like eruption of discrete flat red macules with telangiectases and pigmentation. He connected the dermatosis with colitis and an abundance of streptococci in the stools.

Urticaria seems to be relatively common in colonic disease¹⁰⁷. The author observed the first outbreak of psoriasis in a man of fifty in typical localization immediately after a *colostomy* had been performed because of rectal cancer. The patient remained well for two years but never recovered from his psoriasis. Pruritus without visible skin lesions has been seen in patients with colostomy stomata.



Fig. 377.—Colitis ulcerosa. Female aged 32 years. Multiple kidney shaped rapidly progressing and healing ulcers of the legs. Remains parallelism of course of the severe colitis and the ulcerations. Both subject to psychological influence as demonstrated during the excitements of divorce proceedings. Discoloration of the skin is partly due to gentian violet. (Patient of Dr. Greenberg.)

Treatment—If certain dermatoses are caused by pathological contents of the bowel it seems logical to try to treat such skin lesions by the cleansing of the intestinal canal with laxatives, increased intake of water and enemas. These methods are not much used today. However, in urticaria and pruritus catharsis is worth while trying. The use of saline cathartics seems satisfactory. In spite of the good experiences of some authors¹⁰⁸ colonic irrigation has not become a generally accepted method of treatment. Urticaria, lichen urticatus, pruritus

¹⁰⁶Whitfield A. On a hitherto undescribed Disease of the Skin. Brit. J. Dermat. III 24 3 1932

¹⁰⁷Boeckus H. L. Bank J. and Wilkinson S. A. Neurologic Mucous Colitis. Am. J. M. Sc. 176 813 829 1928

¹⁰⁸Urbach H. Das subaquale Darmbad in der Dermatologie. Arch. f. Dermat. u. Syph. 159 523 540 1930

and toxicodermas seem to be the dermatological indications for the use of this method. The technique is well described by Urbach^{30*} and by Read^{30†}. Large doses of activated charcoal to absorb toxic products in the bowel may be used for the same conditions^{30‡}.

The most important method of treatment consists in the proper diet for which the textbooks of gastroenterology and nutrition may be consulted. Very recently Urbach¹⁶ has presented an excellent modern treatise on the dietary treatment of dermatoses including those of gastrointestinal origin.

[†] ³²Read H. H. Colon c Irrigation Med. Abstr. p. 964, 1944. The Year Book Publishers, Inc. Chicago.

[‡] ³⁷Gzillag J. Dy peptische Hautkrankheiten. Zbl. 35: 337.

CHAPTER XLII

DISEASES OF THE LIVER AND PANCREAS

The Liver

The bile the secretion of the liver contains bile pigments bile salts cholesterol lecithin and mucin¹²⁹ The pigment bilirubin is a waste product from destroyed erythrocytes which have been collected by the reticulo-endothelial system The liver takes bilirubin from the blood and secretes it into the bile Bilirubin which has passed the liver is slightly different from blood bilirubin This is demonstrable by the two van den Bergh reactions Biliverdin is an oxidation product of bilirubin The bile salts facilitate the action of the pancreas and the absorption of fatty acids Cholesterol is a lipid of the sterol group mainly derived from animal fats The liver supplies most of the blood sugar and forms all the urea It synthesizes most of the fibrinogen thus playing an important role in blood coagulation

Liver damage may result in hemorrhagic disease with prolonged clotting time and prothrombinopenia¹³⁰ The liver has a significant detoxifying function Many metabolic and external poisons are either destroyed in the liver or excreted into the bile Disturbance of the detoxifying function of the liver plays an important role in the pathogenesis of allergy The liver is often called the second barrier against poison the first being the intestinal wall^{131 10}

Dermadromes —*Jaundice* may be caused by obstruction in the common duct or in higher parts of the bile duct system provided the dammed up area is large enough The bilirubin is then reabsorbed into the blood There are many causes for such an obstruction the most important being gallstones neoplasms scarring or inflammatory swelling

In *toxic or infective jaundice* the bilirubin secretion of the liver cells is disturbed Therefore the blood cannot be sufficiently freed of its bilirubin which soon reaches an icteric level Toxic or infective jaundice is the most common form of jaundice³⁵ It is encountered in yellow fever Weil's disease typhoid fever pneumonia and other infections in poisonings from chloroform gold arsenobenzol phosphorus carbon tetrachloride some mushrooms e.g. *helvella* and a great variety of other toxic agents

In *hemolytic jaundice* the rate of bilirubin production from destroyed red cells exceeds the capacity of the liver to excrete it The urine as well as the feces retain normal color Some forms of hemolytic icterus are hereditary

These causes of icterus are not always sharply divided Thus e.g. obstruction may lead to absorption of bile but also to infection and damage to the liver

¹²⁹U bach F L b r d l wechsel itig n H i h u gen zwisch n Lebe und Haut Arch f i m rmat u Syph 175 767 787 1937

cells with subsequent failure to drain bilirubin from the blood. Jaundice is probably the most regularly encountered skin manifestation of any internal disorder.

The color of jaundiced skin varies widely from a slightly yellow tinge to lemon greenish brown or even purplish shades. Greenish jaundice is explained by cyanosis; brown or black hues come about by combination with various pigmentations. Orange or saffron color of the skin suggests intrahepatic jaundice, greenish to bronze obstructive jaundice. A greenish tint may develop in intrahepatic jaundice in the presence of liver necrosis and also in the receding stage of jaundice.³⁰⁶ Yellowish blue or green is considered almost diagnostic of a tricuspid lesion or a relative insufficiency of the valve (Wearn after Jeghers³⁰⁸).

The distribution of jaundice is not always even. In slight and early cases only the sclerotics or the hard palate may appear yellow. In catarrhal icterus the discoloration usually appears on the head, neck, the upper trunk, the abdomen, the legs and finally on the forearms and hands.³⁰⁷ The jaundice may come on in repeated attacks, each increasing the color of already yellow areas. At the height of the icterus the areas which appeared first are then the darkest. Thus the upper part of the body is generally darker than the lower part.^{308, 309} The regression of icterus follows the reverse order of its appearance, so that sclerotics and face may still be yellow when all other parts have reached a normal color. The differences in intensity are not yet sufficiently explained. Differences in concentration and in the amount of blood which during a given time flows through and stains the areas are likely to cause difference of intensity of color.

Hyperemia or urticaria causes local increase of the icterus, probably because of greater capillary permeability; this is easy to demonstrate under glass pressure. In subclinical icterus the hyperemic halo of a histamin reaction leaves a yellow ring after the hyperemia has disappeared. With this skin test a bilirubin level of as low as 1 mg. per cent can be shown.³⁰³ The remaining local icterus after disappearance of urticaria factitia is called yellow dermographia.³⁰³ It may be present prior to clinical icterus. Two cases of contralateral jaundice and ipsilateral edema in apoplexy and cardiac decompensation have been described by Page.³¹¹ It has been suggested that in these instances the edema prevented the entrance of the pigment, but this is unlikely since a local edema like a wheal increases icterus.

Localized jaundice about the umbilicus due to rupture of the common bile duct was described by Rauschoff (see Jeghers)³⁰⁵

³⁰⁶ Lichtman III. Diseases of the Liver. Philadelphia 1941. Lea & Febiger.

³⁰⁷ Hoesel F. Über die Verteilung der Galle bei Ikterus. Wchnschr. 1933 II 14 6-14.
(mit F. A. J. Posenberg M. R. Klonke Iktus. D. ut. h. med. Wchnschr. III 90-91)

³⁰⁸ Hoesel F. Die Verteilung der Galle in der Haut beim Ikterus neonatorum. Zt. hr. II Kl. 1938 313-50 1934.

³⁰⁹ Hoesel F. Die Verteilung der Galle in der Haut beim Ikterus neonatorum. Wchnschr. 1933 II 14 6-14.

³¹⁰ Hoesel F. Die Verteilung der Galle in der Haut beim Ikterus neonatorum. Wchnschr. 1933 II 14 6-14.

³¹¹ D. bes. A. J. A. J. Cong. Harit. II F. Yellow Dermographia. Arch. Dermat. & Syph. III 310-311 1943.

Several tests using injection of dyes into the skin have been devised to demonstrate subclinical icterus³⁰²³ but none has become important since accurate quantitative determinations of bilirubin in the serum are now generally made with the van den Bergh method. Intracutaneous injection of 1 per cent potassium ferricyanide produces a blue spot if the icterus is caused by an iron containing blood derivative. This is known as the positive Brugsch test³⁰²⁴. Bilirubin is iron free. The value of the Brugsch test for iron has recently been doubted³⁰²⁵. The extrahepatic type of icterus is seen in the presence of very numerous skin hemorrhages which may cause generalized yellow discoloration. The Brugsch test is also positive in icterus neonatorum.

Itching sometimes restricted to some areas is a common and troublesome though not invariable symptom of icterus. It is absent in hemolytic icterus³⁰²⁶. It is controversial whether the presence of bile salts and bilirubin is responsible for the pruritus. Insulin in doses of 20-50 units daily seems to relieve the itching³⁰²⁸. In senile and other types of pruritus sine materia tests sometimes indicate an impaired liver function³⁰²⁷.

The capillaries of icteric skin are more permeable than those in the normal skin.

Urticaria is frequently seen. The icteric skin develops a wheal after injection or iontophoresis of a one hundred times weaker histamin solution than is necessary to create the same effect in the normal skin¹⁰⁰⁰. Cantharides draw blisters in a shorter time in icteric than in normal skin³⁰²⁸.

The disappearing time of an intracutaneous wheal of isotonic salt solution (McClure and Aldrich Test¹⁰⁰⁰) is shortened in icterus³⁰²⁹.

Long lasting jaundice with hypercholesterolemia as in biliary cirrhosis may produce *xanthomas* in the skin. One has to look for these lesions in the creases of the finger joints and about the elbows. These xanthomas are reversible with changes in the blood cholesterol³⁰³⁰.

✓*Liver spots* are chloasma like hyperpigmentations in the face caused by melanin deposits. They are suggestive of liver disease but are neither frequent nor specific. The French term *masque biliaire* is applied to a periorcular chloasma hepaticum.

The *hemorrhagic tendency*³⁰⁴ may be severe, however it is not parallel to the icteric indexes³⁰⁰. It constitutes an added risk in any surgery on a jaundiced patient. Gastrointestinal bleeding is usually the first hemorrhagic symptom in obstructive jaundice. An alarming picture of hemorrhagic disease

³⁰²³Dadlani C. Sulla Icteria e della bilirubina nella pelle degli itterici. Riv. di clin. med. 22, 501-506 1931.

³⁰²⁴Bugha T. Zu Analyse des Ikterus. Deutsch. med. Wochenschr. 19, 91, 697-698.

³⁰²⁵Roenthal F. Hautjucke bei Ikterus. Th. rap. d. G. genev. 70, 297-301, 1931.

³⁰²⁶Malasouli T. In ulnis helmi Pruritus. Ikterus kra. ken. Pensa med. a. gent. 17, 1, 31-1935.

³⁰²⁷Hilner K. Hyperbilirubinemia Icterus. Arch. f. Dermat. u. Syph. 275, 509-514, 1937.

³⁰²⁸D. Tullio R. La permealita capillare in icterus infiammatorio della cute negli epato. Int. Riforma med. 44, 341-344, 1934.

³⁰²⁹Mo. J. M. and J. K. F. J. The Effect of Jaundice on Intracutaneously Injected Salt Solution. J. Lab. & Clin. Med. 20, 719-722, 1933.

³⁰³⁰Comf. M. W. Shepa. d. V. O. and G. H. A. M. Xanthomatous Biliary Cirrhosis. Proc. Staff Met. Mayo Clin. 18, 3, 377, 1941.

may follow.²⁰⁰ Quick emphasizes the absence of petechiae and the presence of large ecchymotic areas.

The lack of vitamin K which maintains the normal level of serum prothrombin is now recognized as the cause of the hemorrhagic disease in obstructive jaundice with not too much damage to the liver.²⁰⁰⁻²⁰¹

Extensive liver damage whether primary or secondary may account for the inability of the liver to produce prothrombin. The resulting hemorrhagic tendency is due to hypoprothrombinemia and is not relieved by vitamin K.²⁰⁰⁻²⁷⁰

Cirrhosis of the Liver—In portal cirrhosis the skin is usually grayish or sallow. Icterus often little pronounced is seen in 30 to 65 per cent of the cases.²⁰¹⁻²⁰³ Pruritus is common. Urbach²⁰⁷ has produced considerable evidence



Fig. 35.—Cirrhosis of the liver. Large ascular capillaries with basophilic nuclei, small portal tracts. (Forness and W.B. Medicine.)

tracing the pruritus in hepatic cirrhosis to the disturbed protein metabolism of the liver. While there are no conspicuous dermatomes, the frequent appearance of spider-like telangiectases is of theoretical and to some extent prognostic interest.

Wass, R.R.: The Diagnosis and Treatment of the Purpale Diseases. South M. J. 24: 56-61, 1931.

Bagl, J.D.: A Clinical Study of the Cases of Cirrhosis of the Liver. N. Y. M. J. 21: 1244, 1914.

Latn, R.O.D.: Histology of the Liver. The Natural History of Liver Cirrhosis of the Liver. Analysis of 36 Cases. N. Y. M. J. 1912.

PLATE VI

- 1 Herpes simplex as seen in many fevers
- 2 Hepatic cirrhosis \ cite congested veins axillary alopecia pigmented male nipple
Note absence of striae
- 3 Hepatic cirrhosis Erythema of the palmar eminences o called liver palm and vascular
spider in unusual location
- 4 Hepatic cirrhosis Vascular spider
- 5 Biliary cirrhosis Four years after ligation of common duct jaundice
- 6 Biliary cirrhosis Bleeding gums decayed teeth

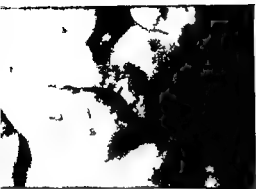


PLATE VI

Vascular spiders (cutaneous arterial spiders³⁰⁴¹ *nevus araneus* like or stellate lesions *tache stellaire* *toile vasculaire*) were first described in an alcoholic (hepatic cirrhosis) by Erasmus Wilson³⁰⁴¹. Their physiology, histology and clinical significance has recently been studied by Patek, Jr., Post and Victor³⁰⁴², Bean³⁰⁴³ and many other authors particularly French.

The vascular spider consists of a body which is a central raised pin head to lentil sized papule from which the legs, spokes or radicles radiate. The latter are telangiectases which branch out and anastomose in many ways. An area of erythema often surrounds the central punctum and an anemic halo around the red area is occasionally visible. The color of the central eminence is bright red but does not show well in infra red photography³⁰⁴⁴ which is one of the proofs of its arterial nature. Veins appear darker in infra red. The temperature of the vascular spider is 2-3° C (3-5° F) higher than the normal skin surface. The blood flows from the center to the periphery and pulsation can usually be demonstrated if controlled glass pressure is applied. The intravascular pressure as measured by the force necessary to stop the pulsation and blanch the lesion is between 70 and 90 mm. of Hg. Adrenalin blanches the finer ramifications and histamine deepens the red area more than the adjacent skin. The number of spiders varies from a single one to an occasional exanthem of the density of mild chicken pox. This however is rare. The spiders are with few exceptions restricted to the upper half of the body with a predilection for the neck, clavicular areas and face. The pattern of distribution reminds of sites of benign new growths under estrogenic influence (see pregnancy and menopause). The palms are more often affected than the arms. Scattered or reticular fine telangiectases may be seen together with the spiders indicating the widespread alteration of the capillaries. Bean³⁰⁴⁴ aptly compares this type of telangiectasis with paper money flecked with silk threads.

Besides the *nevus araneus* like lesions simple telangiectases in small plaques at the costal arch were described by Galloway³⁰⁴⁷ in various visceral conditions with stasis including cirrhosis.

Stellate telangiectases in cases of Laennec's cirrhosis have been found in 15 per cent by Ratnoff and Patek³⁰⁴⁵, 56 per cent by Ciromacki (after Bean) and 75 per cent by Bean³⁰⁴⁴ but they are also encountered in other liver diseases e.g. in catarrhal jaundice in Weil's disease and in common duct stone with jaundice though decidedly less often³⁰⁴⁶. The chronicity of the disease does not seem to have much bearing on their development since they have rarely been found in hepatic carcinomatosis. It can generally be said that the presence of spiders indicates a more severe cirrhosis³⁰⁴⁴. Improvement of the hepatic condition may be followed by disappearance of the spiders.

The histological^{3044, 30, 3049} character of the spider is that of a coiled artery larger than that ordinarily found in the surface of the skin. The arterial wall has

³⁰⁴¹ Erasmus Wilson, *The Cutaneous Arterial Spider*, *Amer. J. Med. Sci.* 1913-331, 1914.

³⁰⁴² Patek, Jr., Ervitt, *Angioma of Cut. Med. & Dis.* 1941, 1, 2.

³⁰⁴³ Patek, A. J., Jr., *Int. J. Nephrol. & Urol.* 1941, 1, 1. *Vascular Spider Associated With Cirrhosis of the Liver*, *Amer. J. Med. Sci.* 200, 341-34, 1940.

³⁰⁴⁴ Galloway, J., *Med. J.* 1941, 1, 1. *Visceral Disease First Met. J.* 1940, 1, 60-66.

³⁰⁴⁵ Wegell, C., *Cirrhosis of the Liver With Telangiectases of the Skin*, *Schw. Ig. Ztschr.* 1941, 1, 374-3.

some characteristics of the arterial segment of an arteriovenous anastomosis (glomus). The spider is decidedly different from a hemangioma.

The free urinary *estrogen* values in advanced cirrhosis are high and the androgen values are low.¹⁴¹⁰ The diseased liver seems unable to inactivate



Fig 370 —Hepatic cirrho is gynecomastia



Fig 380 —Hepatic cirrh is pigment dark large male nipple

estrogens³⁰⁴⁹ and the testicular atrophy which is common in fully developed cases probably accounts in part for the lack of androgens. Androgens continue to be inactivated by a liver which has been damaged enough to be unable to inactivate estrogens. Thus the balance between estrogens and androgens is upset.³⁰⁴⁹ These endocrine disturbances help to explain the production of spiders, palmar erythema and chloasma which also occur in pregnancy and which can be provoked by administration of estrogens to cirrhotic patients.³⁰⁵⁰⁻³⁰⁵² The low level of androgens may increase the effect of the high estrogens. This may also account for the gynecomastia



Fig 361—Hypertrophy of the areola: Axillary areola enlarged areola nipple

comastia which is frequently present in advanced cases. Paula³⁰ found gynecomastia with increase of milk ducts, cyst formation and milk secretion in 5 out of 7 autopsies.¹⁴¹⁹⁻¹⁴²¹ The nipples are often enlarged, cylindric and erect, the areola deeply pigmented. The loss of axillary and to a lesser extent pubic hair³⁰⁵³ is common in cirrhosis. This symptom may also be related to endocrine disturbances, especially testicular.

³⁰⁴⁹Blockstein M S, Blockstein R and Blockstein H. Nutrition and Diet in the Etiology of Malnutrition. Malnutrition: Cystic Mastitis and Premenstrual Tension. II. Treatment with Vitamin D. *Comp Surg Cytor & Oncol* 78:49-7, 1914.

³⁰⁵⁰Hean W B. A Note on the Etiology of Cutaneous Atelectasis and Palmar Erythema in Liver Disease and Their Treatment Following the Administration of Furosemide. *Am J Med Sci* 205:1-3, 1914.

³⁰⁵¹Hean W B. A Generalized Palmar Erythema and Cutaneous Vasculitis. *Am Heart J* 25:463-477, 1913.

³⁰⁵²Paula E. Gynecomastia und Leberzirrhose. *Deutsches Arch für klin Med* 169:83-99, 1930.

³⁰⁵³Mertel F. Spontaneous axillary alopecia in liver disease. *Ann Intern Med* 51:4, 1931. 211:29, 764.

Erythema of the palmar eminences (liver palms) especially of the hypothenar often associated with spiders was observed in about 25 per cent of the patients with cirrhosis³⁰⁴ but only in 4 per cent of Ratoff and Patek's³⁰¹³ 386 cases. The condition also occurs in other internal disorders e.g. gastrointestinal ulcer, rheumatoid arthritis, heart disease, chronic sepsis, pulmonary tuberculosis, chronic deficiency states and in pregnancy. It is also occasionally seen in normal persons. Palmar erythema like its related lesion the vascular spider may wax and wane with fluctuations in the severity of the liver disease.³⁰¹¹ It has been



Fig. 38. —Hepatic cirrhosis axilla y alopecia. Male aged 50 years

shown that palmar erythema can be provoked by potent estrogens in persons having some of the mentioned diseases.³⁰⁴ The erythema is arterial in character and warm to the touch. The capillaries are increased. The palmar erythema is sometimes combined with erythema of the fingertips, clubbing of the end phalanges and Hippocratic nails.

The well known appearance of *dilated veins* around the navel (*caput medusae*) is relatively rare. Congested veins are of frequent occurrence in the presence

³⁰⁴Perera, G. A.: A Note on Palmar Erythema (So Called Liver Palms). J. A. M. A. 119: 1417, 1943.

of ascites³⁰⁴². In more than 40 per cent of the cases³⁰⁴ dilated veins in the skin of the abdominal and thoracic walls show the existence of an established collateral circulation. Infra red photography may detect tortuous veins before they become visible. Edema of the ankles occurs in the majority of the cases. Hemorrhoids are seen more frequently in cirrhosis than in comparable groups (Chapman Snell and Rowntree after Ratnoff and Fatek³⁰⁴³). Hemorrhagic phenomena are observed in about 25 per cent of the



Fig. 381 - Biliary cirrhosis. Skin to gate



Fig. 382 - Xanthoma. Bilirubinemia in patient with biliary cirrhosis

cases of cirrhosis. One third of the hemorrhagic patients show purpura³⁰⁴³ Striae are absent

In *biliary cirrhosis* the jaundice is severe. Bleeding from the gums is frequently seen. Xanthomas in the palmar creases the soles and elsewhere may develop in hyperlipemia³⁰⁵⁵



Fig. 38 — Cachexia (biliary cirrhosis). Hippocratic nails

Gallstones and Cholecystitis—Little is known of skin manifestations in diseases of the gallbladder. The infected gallbladder may become a focus of infection and cause cutaneous lesions³⁰⁶. A stone in the common duct may cause icterus with its cutaneous sequelae. Xanthoma, especially of the lower eyelid, salivation, gingivitis, transient yellow or persistent chlorasmatic spots on forehead and cheeks, urticaria³⁰, pruritus and telangiectases are occasional manifestations of chronic cholecystitis³⁰⁹.

The Liver in Dermatoses—Many investigators³⁰⁵⁹ have studied liver functions in skin diseases. This has been done with most of the liver function tests (for a practical appraisal of the liver tests see Ivy and Roth³⁰⁶⁰) especially the two van den Bergh tests, the determination of urobilin and urobilinogen in the urine, blood sugar tolerance tests, galactose, gelatine and water³⁰⁶¹, phenol, tetrachlorophthalein sodium³⁰⁶, Widal's hemoplasia³⁰⁶², Falt's bile tolerance test

³⁰⁴ Easton C. B. and McIntomey H. Disorders of Liver and Extrahepatic Biliary Ducts. Asociat. With Cutaneous Xanthomas and Hyperlipemia. Gastroenterology 3: 275 '36 1944

³⁰⁴¹ La C. W. and Stoud C. M. Isolated Gangrenous Arch. Dermat. & Syph. 27: 460 468 1933

³⁰⁴² J. J. R. Results of Treatment in Angio-neurotic Edema and Urticaria. J. A. M. A. 90: 664-671 1934

³⁰⁴³ Dal a J. D. Jaundice signs but cause of cutaneous lesions in cholelithiasis. Bull. med. 1931 11: 9 1936 211 41 78

³⁰⁵ Duloway M. I. or I. tion z. i. cl. n. Haut und Leler. Dermatologi a 79: 370-391 1939

³⁰⁶⁰ Ivy A. C. and Roth J. A. Why do a Liver Function Test? Gastroenterology 1: 655-669 1943

³⁰⁶¹ D. H. n. H. L. f. fu. k. i. p. i. fu. k. in d. r. Dermatologi Arch. f. Dermat. u. Syph. 168 49: 504 1933 180 450 463 1934

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and the determination of urobilinogen in the stools after Schmidt³⁰⁹ Other investigations were concerned with the reticulo-endothelial system of which the Kupffer cells in the liver represent an important part The disappearance of intravenously injected congo red from the blood (Adler and Reimann test) was used as an indication of the function of the reticulo endothelial system in the liver³⁰⁸⁹ The reticulo endothelial system of the skin was studied in this connection by von Leszczynski and his collaborators³⁰⁹ mostly with intracutaneous injections of histamin morphin caffeine pilocarpin and trypan blue The results of the many investigations of liver function in dermatoses are not consistent Hepatic dysfunctions were found in eczema^{306 3064 3068} acute exudative dermatoses³⁰⁶¹ urticaria dermatitis after arsphenamines^{0 5 3061 3063} and other drug eruptions³⁰⁶⁷ In the larger series the patients with disturbances ranged from 10 to 40 per cent The high incidence of liver disorders in photodermatoses drug eruptions rosacea and other dermatoses characterized by widespread new formation of capillaries is emphasized by Milbradt³⁰⁶⁴ and many others

Porphyria and increased fecal porphyrin which often accompany photodermatoses e.g. hydroa vacciniforme is probably the expression of a disturbed liver function^{30 3070 3072} The combination of alcoholism and syphilis is apt to create the conditions which lead to hepatic cirrhosis porphyria and photodermatosis In porphyria and hydroa the mechanical vulnerability of the skin may be much increased so that slight trauma may cause blisters and oozing defects^{307 3072} Thus an epidermolysis bullosa like picture may ensue^{3074 3076} Photodermatoses with an hepatic background and hyperporphyria or porphyria may also appear as xeroderma pigmentosum³⁰⁷⁷ eczema urticaria erythema multiforme and prurigo

Xanthomas including the common xanthelasmas of the eyelids should always arouse the suspicion of liver disease Icterus is frequently found in xanthoma and even in its absence liver disorders may well be detected by function tests (Hubner after Urbach³⁰⁸)

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³¹ordowich F "Blutstirubi bestimungen i i Haut ank h n Ar h f D rmat u G yph

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³⁰⁴quardt Porphy in im U l n b i Haut krankung n Zil 83 5 3-6 1936

³⁰⁴Milbradt W "U und Org astör g n L b rstoffwech i Med Welt 9 1417 14 1 1935

³⁰⁶Carri C "Hydroa a infirm uni Po l y r i n u r i c A ch f De mat u G yph 163 5 3-43

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34 Arch Dermat & G yph 29 91-30 1919

³⁰⁷l rba h F "H i o a cci f r m l Leber und Milacirrhose P phyri u i Zil 63 149

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³⁰⁷Turner W J and Oberm y e M F "P r p h y i a W i t h E p i l m o l y i f l l o a H y p e r t e i s i

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"B l u m l b a l "X e r o d e r m a p i g m t o s u m a v e c E p i t h l o m a d t y p e s d i v e r s e Blut F u r

D r m t 2 74 6 1931 Zil 29 "

³⁰⁷l rba h F "h w t e L i c h t l m a t o s e n a u f G r u d i a g v o n b e l l e r t r p a t h o l g i e l e i s i j l p r l

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Clinical experience has often shown that psoriasis eczema urticaria^{305 3057 3079} Quincke's edema rosacea and other dermatoses followed the ups and downs of liver or gallbladder disease and cleared up after their successful treatment. An impressive group of such cases was presented by Smithies³⁰⁸⁰ who used drainage of the duodenum mostly combined with a diet low in fat and protein and stimulation of the flow of bile by magnesium sulfate.

The opinions about associated liver disturbances in psoriasis are divergent.^{3061,3063} The possibility of liver damage secondary to skin disease must be recognized. This is based on observations in burns and in the experimental croton oil dermatitis of rabbits.³⁰⁶ Dubow³⁰⁵⁹ found hepatic dysfunction regularly connected with a disturbed RES of the skin.

Liver extract has been found a useful adjunct in the treatment of many skin diseases.³⁰⁷³ Exfoliative dermatitis due to arsphenamine is an example.

The Pancreas

The pancreatic juice neutralizes the gastric acidity, splits proteins down to amino acids (trypsin), fats into glycerine and fatty acids (lipase) and converts starches into sugar (amylase). The best known hormone of the pancreas is insulin which helps to burn sugar, stimulates the formation of glycogen in the liver and muscles and probably inhibits glucose formation from amino acids in the liver.¹²³⁹ In pancreatectomized dogs the liver becomes fatty. This can be prevented by an alcoholic extract of pancreas. Dragstedt's lipocain¹⁹³³

Kallikrein (padutin) is a pancreatic hormone with a vasodilating effect. It can to some degree neutralize the effect of adrenalin. The most important skin manifestations of pancreatic disorders are those occurring in diabetes (see chapter on diabetes). Our knowledge of other pancreatic dermatoses is scanty.

Dermatomes of Pancreatic Diseases—Chronic pancreatitis and other benign disorders may provoke urticaria³⁰⁶¹ eczema pruritus ani³⁰⁸ and other nonspecific dermatoses. The disturbance of fat digestion has been related to some cases of eczema³⁰⁶³ especially in infants.³⁰⁶¹ The administration of pancreatic substance by mouth has been recommended.

Acute necrosis of the pancreas (acute pancreatitis) is occasionally accompanied by deeply cyanotic livedo like or spotty venous patterns (Vahsted after Moynihan³⁰⁸) covering the abdomen, chest and thighs.³⁰⁸⁶ A palm sized dirty

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³⁰⁶⁴ Rueda P. Fecomas et s. borrlhes du n. urri o. S. mana med. 30: 81-96, 1933. Zbl. 12: 60.

³⁰⁶⁵ Moynihan B. Acute Pancreatitis. Ann. Surg. 81: 13-14, 1925.

³⁰⁸⁶ Walz I. Symptom der flecken und gitterförmigen Cyanose bei acuter Pankreasnekrose. Wien. klin. Wchnsch. 40: 216, 1913/7.

gray green slightly raised discoloration has been observed around the navel or in the lumbar area probably caused by direct leakage and autodigestion. This is known as *Turner's sign*^{3085 3087 3088}. The abdominal cyanosis is not seen in the majority of the cases³⁰⁸⁹. It is considered a pathognomonic sign.

Cancer of the head of the pancreas causes intense obstructive sometimes blackish jaundice (ictère noir)¹⁸⁷⁸. In 56 per cent of the autopsied cases of cancer of the body or tail of the pancreas at least one thrombosis was found³⁰⁹⁰. In about one third of the cases the venous thromboses were widely disseminated. Usually there was no jaundice present. Thromboses of veins in both lower legs with acute cutaneous inflammation may be the presenting symptom of carcinoma of the pancreatic body³⁰⁹¹. No mention of thromboses is made in a recent review of 52 cases of pancreatic carcinoma³⁰⁹. The thromboses may affect any of the great veins of the body. The neoplasms were all of the mucinous type.

Pancreatic extracts especially lipocaine and depropanex have given encouraging though not striking results in psoriasis^{3092 3093}.

The insulin free pancreatic extract padutin or kallikrein³⁰⁹⁴ and similar preparations¹⁹⁸⁸ has been used in Raynaud's disease acrocyanosis and related peripheral vascular disorders. It has also given some results in scleroderma³⁰⁹⁵ of the morphea type.

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CHAPTER XLIII

DISORDERS OF THE RESPIRATORY TRACT*

Generally the incidence of dermatoses in very large numbers of institutionalized pulmonary patients was below the average of the general population.¹⁰⁵ This seems to be due to the sheltered life and the absence of occupational hazards.

Cyanosis is marked in many respiratory diseases. The blue discoloration may be of short duration as for example in the whooping cough attack or it may be longer as in diphtheria. Some cases of pneumonia, pleuritis, emphysema or large mediastinal tumors.

The frequency of acrocyanosis and erythrocyanosis in a series of about 5000 cases of pulmonary tuberculosis is emphasized by Szanto.^{744, 8017} Papulonecrotic and indurative tuberculous lesions have been described in connection with acrocyanosis^{3009, 3009} and livedo racemosa.¹ Women are particularly subject to acrocyanotic conditions which may account for the female dominance in tuberculosis indurativa (erythema induratum).

Telangiectases on the thorax are said to occur in 45 per cent of patients with pulmonary tuberculosis. They are called *Francke's striae* a misnomer since they are actually telangiectases and not atrophies.^{647, 745, 8100}

These telangiectases are at most 1 cm. long straight curved or branched thin sharply drawn blood vessels in the skin over the upper dorsal vertebrae and along the costal arch in front of the anterior axillary line. The latter are much more common than (11 per cent) the former about equally frequent (3 per cent) in both sexes.⁷⁴⁵ *Francke's striae* seem to be independent of the severity of the lung process but more apt to occur in cases of long duration. They are probably due to lung and pleural involvement adjacent to or underlying the respective skin areas. The telangiectases are not characteristic of tuberculosis since they are encountered in normal persons and also in emphysema. They are common in elderly men.

Sorgo³¹⁰¹ found the skin over parietal pleuritic lesions thicker and slightly edematous. It is consistent with the observation that hypodermic injections of 1 per cent solution of congo red into symmetric sites of the thorax showed in 36 out of one hundred patients with pulmonary tuberculosis a larger spot on the diseased side.³¹¹

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³¹⁰⁰Howard C. F. i. l. a. n. i. a. s. u. s. e. l. e. t. a. l. i. n. i. t. u. b. i. l. i. R. i. v. d. i. p. a. t. u. e. l. l. i. d. i. t. u. t. e.
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⁸¹⁰¹Goldstein M. F. a. i. g. i. s. i. t. u. l. u. g. d. e. q. g. o. h. e. n. H. a. u. t. f. a. l. t. e. n. p. h. n. o. m. n. a. W. i. n. k. i. n.
 Wechnach. 1935 i. 36

Striae thoracicae in lung disease have been discussed under the heading *striae*

A rapid course in pulmonary tuberculosis often increases the *succulence* of the skin. In chronic cases the skin is more apt to be thin and dry—even diffusely atrophic resembling senile skin. Szantó⁷⁴⁸ considers these changes as nonspecific and inherent to the severe disease.

Fungus diseases are frequent. *Pityriasis versicolor* once considered a characteristic accompaniment of pulmonary tuberculosis has become relatively rare. 1.5 per cent.⁷⁴⁸ This is probably due to better bathing conditions. However it is still three times more frequent among the dermatoses of the inmates of lung sanitariums than among the dermatoses of nontuberculous groups. The incidence of epidermophytosis is 6 times greater⁷⁴⁸ sweating probably being a factor.

Many statistics emphasize the high incidence of *acne* among the patients of lung sanitariums. The percentages range from 7 per cent³¹⁰ over 12 per cent⁷⁴⁸ to about 40 per cent.^{747, 3103} However these statistics lack comparable controls in the corresponding age classes of the healthy population. Overeating of fats during dietetic treatment may be responsible. The more severe *acne dorsalis* is often found over the site of the greatest pulmonary involvement.^{747, 748} Szantó⁷⁴⁸ in his very large series confirms the relatively great frequency, severity and incidence in age groups up to 40 and 50 years. Exacerbation of *acne* after artificial pneumothorax has been observed by several authors.^{747, 748} Shoji³¹⁰⁴ found the eyelashes of patients with pulmonary tuberculosis to be longer than those of normal controls. Chloasma was found twelve times more frequently than in the general population.⁷⁴⁸

Since it had been suspected that pulmonary tuberculosis in *red haired* persons takes a more rapidly fatal course Bogen³¹⁰⁵ compared a group of red haired persons with the average of 10 000 other patients with pulmonary tuberculosis. No significant differences in the fatality rate could be found.

The pressure in the *skin capillaries* was found higher in fibrotic pulmonary tuberculosis than in exudative forms.³¹⁰⁶ In a series of 241 cases of pulmonary tuberculosis the capillaries of the nailbeds of the fingers on the side of the more active lung lesion were found more dilated than on the other side. The side of gross fibrosis and caverns is often marked by deformed capillaries on an anemic background.³¹⁰⁷

Bronchial asthma is sometimes combined with eczema of the flexor surfaces. Alternating between eczema and asthma also familial accumulations of both

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conditions is well known. The discussion of these relations belongs to the province of allergy.

The lunulae of the *fingernails* were found absent from all fingernails five times more frequently in patients with pulmonary tuberculosis than in controls and eleven times more often when the tuberculosis was complicated by silicosis.²¹⁰⁸ Heller considers the disappearance of the lunulae an important diagnostic and prognostic sign but it is not rarely seen in healthy person.

Clubbing of the fingertips often accompanies chronic pulmonary lesions e.g. emphysema, pulmonary abscess, bronchiectasis and carcinoma.²¹⁰⁹ Clubbing occurs in 17 per cent of cases of chronic pulmonary tuberculosis. It seems more



Fig. 84c.—Clubbed fingers bronchiectasis.

common in Negro males than in whites and it indicates a poor prognosis.²¹⁰⁹ The terminal phalanges become thicker and the nails larger and curved in both the longitudinal and transverse directions.

Pitting of the nails was observed in 100 per cent of a group of patients suffering from active pulmonary tuberculosis as compared with 6 per cent of a group of patients whose disease had been inactive for a relatively short period. It was completely absent in patients who were inactive for longer than one year.²¹¹⁰

Frequent dermatomes of pulmonary tuberculosis are *thickening of the nail plate and longitudinal curving*. The latter is known as the *Hippocratic nail* because Hippocrates knew and described the curved nail and its ominous prognostic significance. Modern observations^{2111, 2112} have amply confirmed the high

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²¹⁰⁹ Kaplan, H. H. and Muios, L. Clubbed fingers in pulmonary tuberculosis. Am. Rev. Tuberc. 44: 439-450 (1931).

²¹¹⁰ Hahn, A. G. Curving of the Fingernails in pulmonary tuberculosis. Am. J. Tuberc. 20: 870-891 (1931).

incidence (76 per cent³¹¹⁰) of Hippocratic curvature in active cases. Szantó⁷⁴³ however found only 5.6 per cent among 27,540 patients.

Cyanosis of the distal end of the fingernail bed was noted in 66 per cent of Hahn's group and in 4.2 per cent of Szantó's group of active cases. Differences in the severity of the cases of pulmonary tuberculosis seem to explain the great discrepancy. The cyanosis of the nailbeds is more pronounced in rapidly advancing cases. Ridging transverse and longitudinal does not seem to be of prognostic importance.⁷⁴⁸

TABLE II DIFFUSE PIGMENTATIONS

CAUSE	DISTRIBUTION	COLOR	MUCOSAE	ASSOCIATED SYMPTOMS	BLOOD	URINE	PIGMENT	HISTORY COURSE	MICELLANTO'S
Addison's Disease	Uneven emphasis on normally pigmented areas face neck hands palm nail beds light creases dark	Gray-tan	Slate spots common	Asthma hypotension dehydration effect of NaCl and certain thin skin	Hypochromia Low NaCl	High NaCl	Melanin in basal layer of epidermis also in cutis (melanophores)	(brown with acute attacks	TH in 90%, sears pigmented areas of pubic and axillary hair Depigmentation rare Great variability
Exophthalmic Goiter	Addisonian type + chloasma	All degrees	Rare	Vitahige about 10%					
Malaria	Addisonian type	(gray) tan	Rare	Splenomegaly anemia	Miasmodia?				Melanin dermal in 15% mostly milium
Tuberculous	Nipples axillae chloasma Also Addisonian type	Brown	Rare	Cachexia					Rare
Purpuric and other anemias Also Sprue Pellagra	Addisonian type diffuse in a few per cent	All shades to deep bronzing	Rare	In sprue also patches and small pigm. spots besides generalized melanoderma			Melanin and iron containing pigment	Pigmentation exaggerated by exposure to sun	
Abundant Disease	Uneven patchy back belt covered areas more involved than hands or arms	Gray	Occasionally slate spots on buccal mucosa and tongue	Slightly lowered or normal blood pressure Slightly depressed excretions Thick skin etc		Albuminuria common		Vagueness neglected Melanoderma heals quickly under hospital care	Common Diffuse and severe melanoderma rare
	All areas which are able to form increased pigmentation esp face (chloasma) linea alba vulva areola mammae						Melanin		

Substrata in menarche	Similar as in pregnancy			Depression			Mild
Ovarian Tumors	Same						Common
Hepatic (with or without)	Some tend to be in pigmented areas (nipples etc.)						Rare
Pushing down	Central vulvar type is infant face	Dark spots		Obesity strabismus etc.		Melanin except for hemosiderin in hemorrhagic lesions	Rare
Laminar	Largely frequent	Dull slate	Conjunctivae upper half	Ichthyoderma night blindness keratomalacia		Melanin and hemosiderin	Rare
Scurvy (Vit. C)	Diffuse	Generally mild pigmentation				Disappears in treatment with vitamin C	Rare
Hemochromatosis (if used in testes)	Face, genitalia, also large covered areas of trunk	Brown slate often metallic on talc	About 90% basaloid, sclerotic mostly free	Diabetes mellitus Hepatic cirrhosis. Atrophy of testes Alopecia axillaris and pubica		Melanin and iron tanning pigm.	Rare
Ochronosis	Cartilages of ears nose teeth of musculi recti oculorum as triangular bluish spots in interpalpebral fissures	Gray slate-black	Very rare	Circles to black cerumen	Dark or darkening in air	Prolonged absorption of phenol may cause ochronosis	Rare
Acanthosis Nigra	Villous irregular neck with thick lips vulva	Gray black. Rarely non-pigmented	Papillary or granulated appearance of oral mucosa	Visceral cancer in older persons frequently internal (endocrine) arising e.g. obesity diabetes in juveniles		Exposed pigmentation in basal layer	Rare

TABLE II DIVERSE PIGMENTATIONS—Continued

CASE	DISTRIBUTION	COLOR	MICROSC	ASSOCIATED SYMPTOMS	BLOOD	URINE	PIGMENT	HISTORY COURSE	MISCELLANEOUS
Melanoma	Face hands	Bluish black (very rare)							Severe cases extremely rare Slight melanoedema not rare
Idiopathic discoloration	Adipose tissue type			Lymphomas			Melanin		In 10% of the cases
Chronic Circulatory D compensation	Extremities dorsa of hands	Brown		Cyanotic symptoms from decompensation of the cardiac valves and decompensation			Hemoglobin		Produced in cases of cyanosis esp in children
Katzenbach-Schulz-Pfeiffer and other "Racism"	Adipose tissue type Sometimes quite dark Fairly over body	All shades	Spots diffuse or punctate oral and conjunctival pigmentation common in all races inclined to pigmentation (Nigritides, Negroids, terraneans, Jews, Arabs, Japanese etc.)	Occasional parallelism of pigmentation with course of pathosis			Melanin	Ascending	Prodromal cases are rare
Arterio-lymphoma mine	D diffuse or in small patches mixed with depigmentation rhabdomyoma trunk pressure points covered parts generally but not always more affected	Gray brown	Usually free	Keratosis polyneuritis etc		As	Melanin not As	Insidious onset or may not disappear after discontinuation of As	Fowler's solution Drinking water Faints Severe melanoderma may follow exfoliative dermatitis from anhydrous naphthalene

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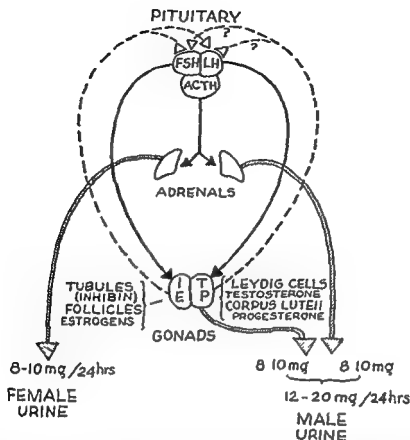


FIG 480 SOURCE OF URINARY 17 KETOSTEROIDS IN MALE AND FEMALE (See also Fig 481) Diagram shows only the immediate factors involved. The mechanism of ACTH and production of S¹ hormones by the adrenal cortices as well as the possible influences of epinephrine and hypothalamus are omitted. The 17 ketosteroids in women are frequently higher than illustrated values of from 15 to 20 mg/24 hrs may be of no clinical significance. Note that all 17 ketosteroids are derived from adrenal cortices while about 50% in males come from the testes.

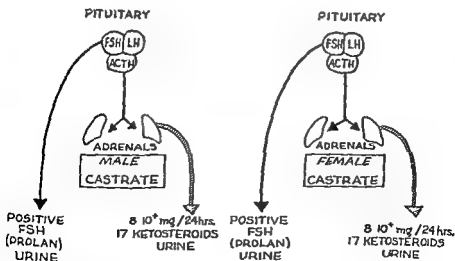


FIG 481 17 KETOSTEROIDS IN CASTRATES 17 ketosteroids in castrated or menopausal women are not significantly changed but are approximately decreased by half in males at least temporarily. Urinary FSH is increased.



FIG 482 EFFECT OF TESTOSTERONE ON DISCOID LUPUS ERYTHEMATOSUS (*Left*) Age 36 Male Biopsy findings were consistent with discoid lupus Testosterone propionate 100 mg daily for 23 days then free testosterone suspension 25 mg intramuscularly daily for 48 days (*Right*) All lesions cleared and improvement has been maintained on 12 mg of testosterone locally for 2 months (Fromer L C The use of testosterone in chronic lupus erythematosus preliminary report Lahey Clin Bull 7 13 14)

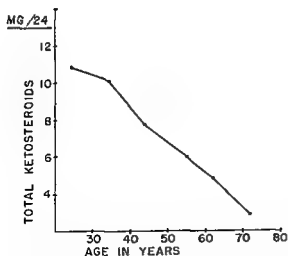


CHART 143 TOTAL 17 KETOSTEROIDS Progressive decrease in the excretion of urinary 17 ketosteroids with aging (Hamilton H M and Hamilton J M Aging in apparently normal men I Urinary titers of ketosteroids and of alpha hydroxy and beta hydroxy ketosteroids J Clin Endocrinol 8 433-452)

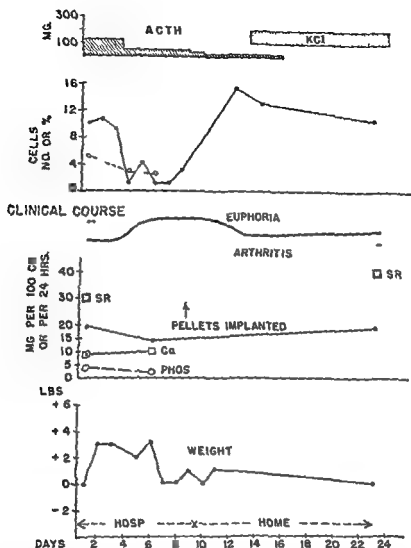


CHART 144 EFFECT OF ACTH IN A PATIENT WITH HYPOPITUITARISM MILD DIABETES INSIPIDUS AND RHEUMATOID ARTHRITIS Age 63 female patient who had an operation for the removal of a crano-pharyngioma about a year before Eosinophils (solid line with black dots) did not fall until fourth day Per cent of lymphocytes (broken line open circles) was also decreased Recurrence of joint symptoms developed slowly after omitting ACTH for several weeks Pellets of testosterone (300 mg) and desoxycorticosterone acetate (150 mg) had previously benefited patient without improving her arthritis All joint symptoms disappeared on readministration of ACTH and patient had been maintained in excellent health on 20 mg ACTH every other day for 6 months when it was discontinued No return of arthritis after 2 years Polydipsia and polyuria (4 to 8 liters daily) were only mildly ameliorated on larger doses of ACTH but on maintenance doses the same amount of pitressin was required to control these symptoms

CHART 145 HEIGHT CHART FOR BOYS
(May Ayres Burgess)

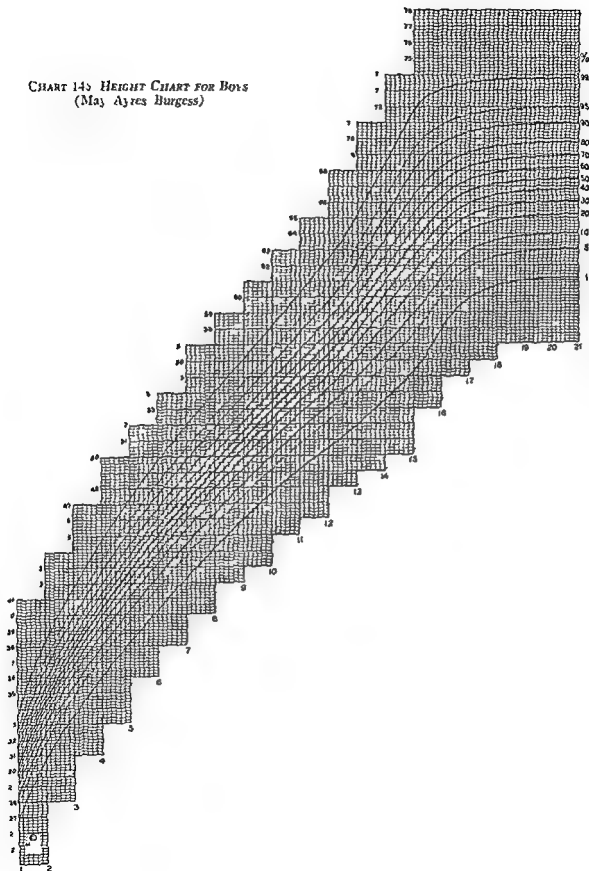


CHART 146 HEIGHT CHART FOR GIRLS
(May Ayres Burgess)

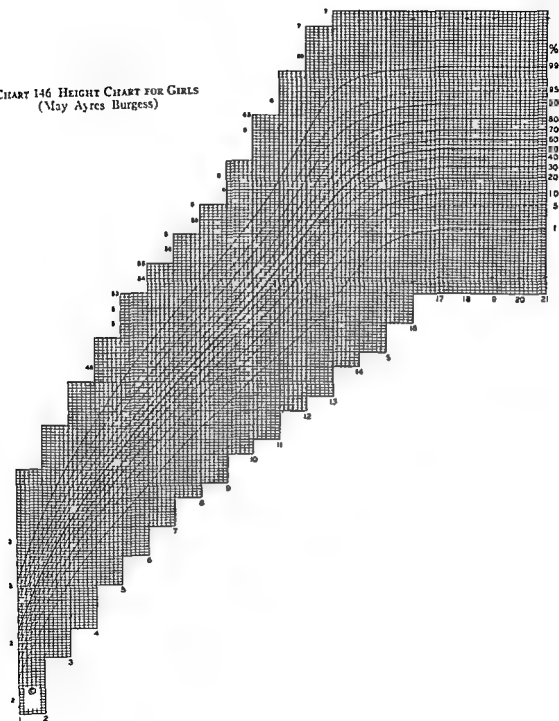
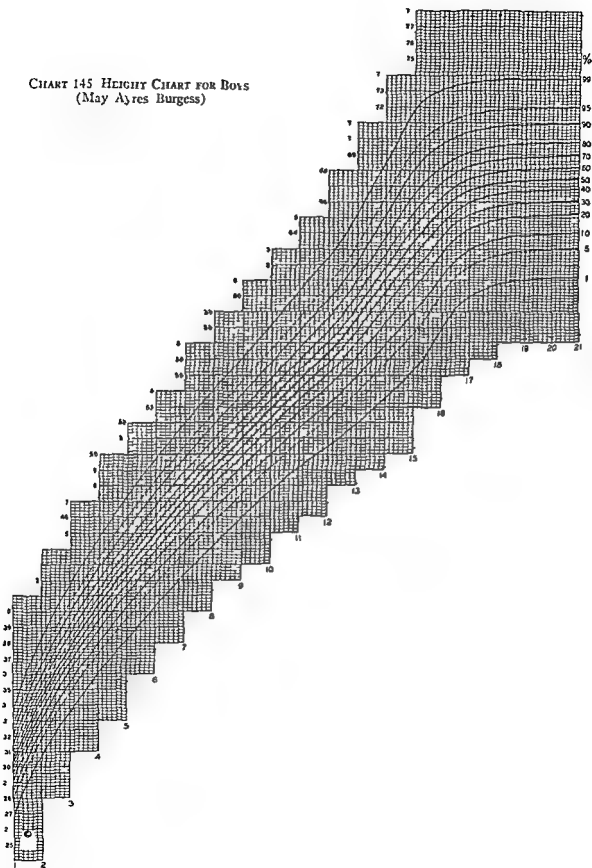


CHART 145 HEIGHT CHART FOR BOYS
(May Ayres Burgess)



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